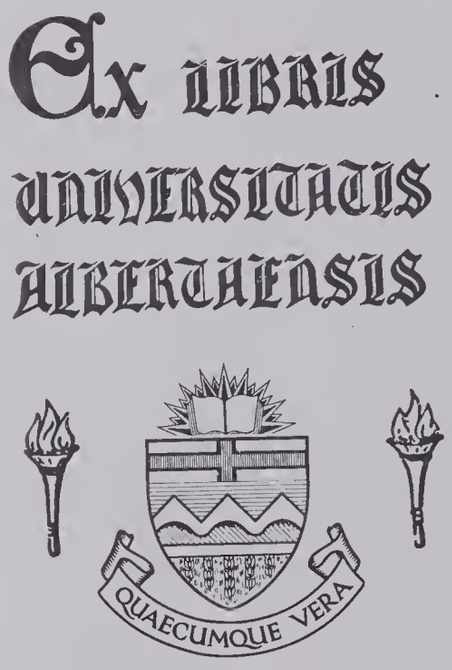
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SUBSTITUTED TETRAHYDROPYRANS

Synthesis of Carbohydrate Analogs

by

FREDERICK SWEET, B.Sc.



A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

MARCH, 1968

UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled

SUBSTITUTED TETRAHYDROPYRANS

Synthesis of Carbohydrate Analogs

submitted by FREDERICK SWEET, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

ABSTRACT

Syntheses leading to the introduction of oxygen at the 2-, 3-, and 4-position of the tetrahydropyran ring have been investigated.

Addition of m-chloroperoxybenzoic acid to a cooled alcoholic solution of 3,4-dihydro-2H-pyran produced trans-2-alkoxy-3-hydroxytetrahydropyrans stereoselectively and in good yields. These compounds could be readily anomerized under acid conditions to give a cis, trans isomeric mixture that was separable by preparative gas-liquid chromatography (g.l.c.). The configurational assignments for the cis- and trans-2-alkoxy-3-hydroxytetrahydropyrans were made on the basis of their nuclear magnetic resonance (n.m.r.) spectra.

Methylation of the trans-2-alkoxy-3-hydroxytetrahydropyrans using sodium hydride and methyl iodide in 1,2-dimethoxyethane gave high yields of the corresponding trans-2-alkoxy-3-methoxytetrahydropyrans.

In the n.m.r. spectra of these trans-2,3-disubstituted tetrahydropyrans, the anomeric (H-2) proton signals appeared as distinct doublets. The magnitude of the couplings ($J_{2,3}$) obtained from these doublets varied with the nature of the C-2 and C-3 substituents. This variation was ascribed to the time-averaged H-2 signal which reflected the different conformational equilibria for each of the trans-2,3-disubstituted tetrahydropyrans.

Cis- and trans-tetrahydropyrano[2,3-b]-1,4-dioxane were prepared and used as models to obtain spin-spin couplings for the trans-diequatorial ($J_{a,a}$) and diaxial ($J_{e,e}$) forms of the trans-2,3-disubstituted tetrahydropyrans. From these values and the observed

couplings ($J_{2,3}$) the conformational equilibria could be estimated. The preference for the trans-diequatorial conformation of the trans-2,3-disubstituted tetrahydropyrans was found to depend on the nature of the C-2 substituent in the order $O\text{-}t\text{-}C_4H_9 > O\text{-}i\text{-}C_3H_7 \geq OC_2H_5 \approx OCH_3$.

Cis- and trans-2,4-dimethoxytetrahydropyran were prepared in high yield by heating 2-methoxy-5,6-dihydro-2H-pyran in acidic methanol. The isomers could be readily separated by preparative g.l.c.. Equilibration of each isomer led to the trans:cis ratio of 4.0:1.0.

N.m.r. data indicated the 4-methoxy group to be in the equatorial position and therefore in the thermodynamically more stable (trans) isomer the 2-methoxy group was axial. The preference of the C-2 methoxy group for the axial position is due to the anomeric effect . The value for the anomeric effect in 2,4-dimethoxytetrahydropyran was calculated to be 1.42 Kcal/mole. This is in contrast to 1.08 Kcal/mole previously found for the anomeric effect in 2-methoxy-4-methyltetrahydropyran. The difference between the two values tends to support the view that the anomeric effect is due largely to intramolecular dipolar interactions since the two compounds differ only in the polarity of the C-4 substituents.

Treatment of a cooled alcoholic solution of 2-methoxymethyl-3,4-dihydro-2H-pyran with m-chloroperoxybenzoic acid produced two isomeric 2-alkoxy-3-hydroxy-6-methoxymethyltetrahydropyrans in the approximate ratio of 80:20. The formation of the preferred isomeric component was felt to be stereoselectively directed by the

2-methoxymethyl group in the olefinic precursor.

Configurational assignments were made on the basis of n.m.r. data. The observed couplings for the H-2 signals of the 2β-alkoxy-3α-hydroxy-6β-methoxymethyltetrahydropyrans indicated the preferred conformation to be that wherein all the substituents were equatorial. There was little variation in $J_{2,3}$ for this isomer when the C-2 OCH_3 group was replaced by O-t-C_4H_9. This shows that the 6-methoxymethyl group biases the pyran ring in the chair conformation in which the C-6 substituent is equatorial.

Treatment of 2-alkoxy-5,6-dihydro-2H-pyran with m-chloroperoxybenzoic acid produced predominately the trans isomer of the 2-alkoxy-3,4-epoxytetrahydropyrans. The observed stereoselectivity in epoxidation was ascribed to steric hindrance by the C-2 alkoxy group to approach by the peroxy acid molecule to the same side of the molecule as is occupied by the substituent. After separation of the cis and trans isomers, each was subjected to $LiAlH_4$ reduction giving exclusively the product resulting from the C-4 oxygen bond cleavage. These results could be rationalized in terms of steric and/or electronic effect. However, it was felt that electronic effects played a major role in C-O bond breaking of the epoxide ring.

Reduction to the known cis or trans 2-alkoxy-3-hydroxytetrahydropyrans was used to establish the configurations of the epoxide precursors.

Correlations made between the established configurations of the 2-alkoxy-3,4-epoxytetrahydropyrans and their n.m.r. spectra lead to assignments of the chemical shifts for protons on the epoxide

ring of 2,3-anhydro-glycopyranosides.

Cis- and/or trans-3,4-epoxy-2-methoxytetrahydropyran was heated in acidic methanol whereupon a mixture of methyl 4-deoxy-3-O-methyl-α,β-DL-threo-pentopyranoside was obtained in good yield. Evidence for the assigned structure of this DL deoxy sugar was obtained by n.m.r. spectroscopy, by its formation of a phenylosazone, and by nitric acid degradation to O-methyl-D,L-tartaric acid. The direction of epoxide ring opening of 3,4-epoxy-2-methoxytetrahydropyran by acid catalysed methanolysis was the same as that found for $LiAlH_4$ reduction.

By applying the knowledge gained from the work described above, methyl 4-deoxy-6-O-methyl-α-DL-arabino-hexopyranoside and 1,6-anhydro-4-deoxy-β-DL-xylo-hexopyranose were stereoselectively prepared from monosubstituted pyran precursors. The di-p-nitrobenzoate of the latter DL compound gave an n.m.r. spectrum identical with that of an authentic sample of the D compound, thus supporting the configurational assignment.

This is believed to be the first reported synthesis of 4-deoxy-DL-pentopyranoses and 4-deoxy-DL-hexopyranoses accomplished by stereoselective elaboration of a monosubstituted pyran ring.

ACKNOWLEDGEMENTS

The author wishes to express his sincere appreciation to Dr. Robert K. Brown, for his guidance and continual encouragement which made this work possible.

Thanks are also extended to:

Mr. Robert N. Swindlehurst, Mr. Glen Bigam, and their associates for infrared and nuclear magnetic resonance spectra.

Mrs. Darlene Mahlow for elemental analyses.

Mrs. Gail Conway and Mrs. Mary Waters for typing this thesis.

The National Research Council of Canada for financial assistance during the summer sessions.

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INTRODUCTION

OBJECTIVES

In the early 1920's Bergmann and Miekeley (1, 2, 3), and Helferich and Malkomes (4, 5) drew attention to certain simple substituted pyrans by demonstrating their chemical similarity to carbohydrates. The fact that these pyrans underwent many of the reactions characteristic of the sugars, established them as carbohydrate models. Since that time this area of organic chemistry has attracted several workers. However, to date the number of successful syntheses leading to oxygen-substituted tetrahydropyrans remains limited.

The primary objective of the work described in this thesis was to develop syntheses leading to oxygen-substituted tetrahydropyrans. It was hoped that compounds obtained from these syntheses would serve as useful models of carbohydrates.

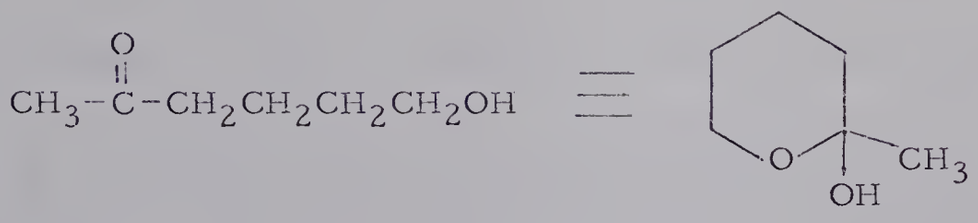
A second objective was to gain more information concerning the stereochemical and electronic factors which governed the chemistry of the pyran ring, and its homologues.

A third objective was to apply the methods developed for the preparation of simple substituted pyrans to the synthesis of carbohydrates.

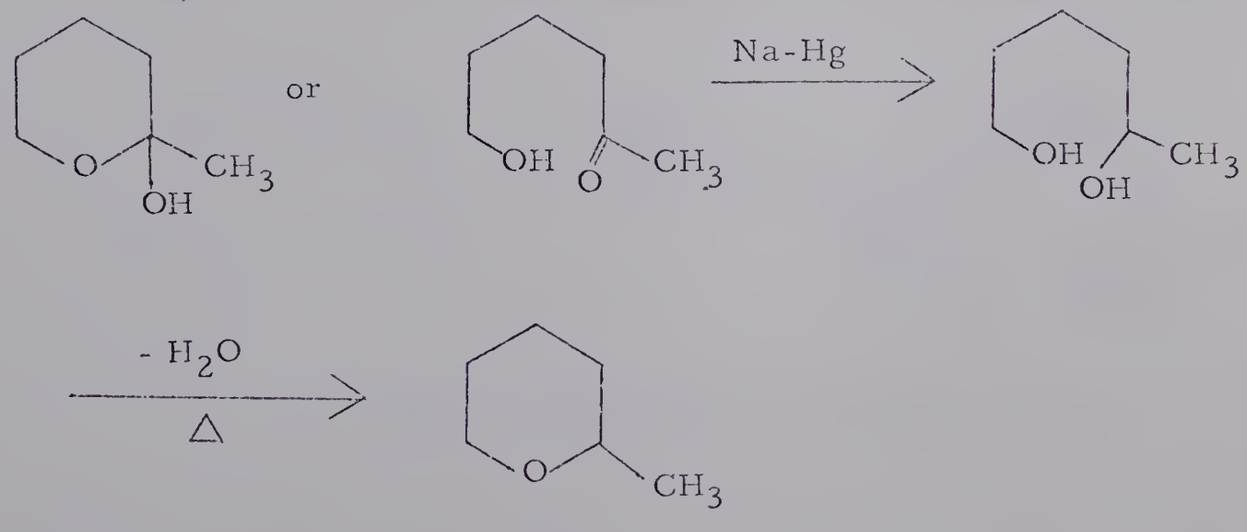
LITERATURE SURVEY

The synthesis of a carbohydrate model preceded evidence for the fact that glucose possesses a six-membered ring structure. Though Tollens (6) in 1888 and Fischer (7) in 1893 suggested simple sugars might have a cyclic structure, it remained until the mid-twenties (8, 9, 10) for strong evidence to be presented in support of this fact.

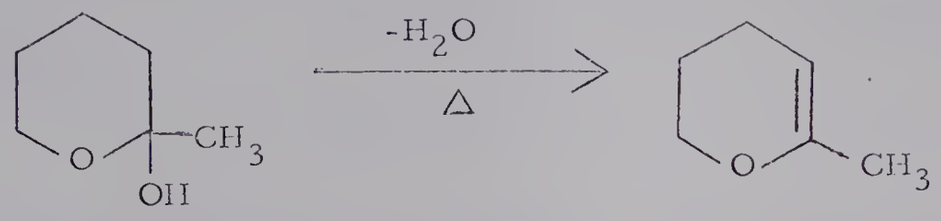
Lipp (11) in 1885 laid the groundwork for synthesis of carbohydrate models by preparing "acetobutyl alcohol" (6-hydroxy-2-hexanone). Reduction of the ketonic function with sodium



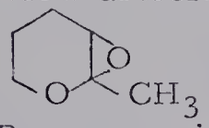
amalgam and dehydration of the resulting diol gave an "amylene oxide", whose structure was correctly assigned by Lipp (11).

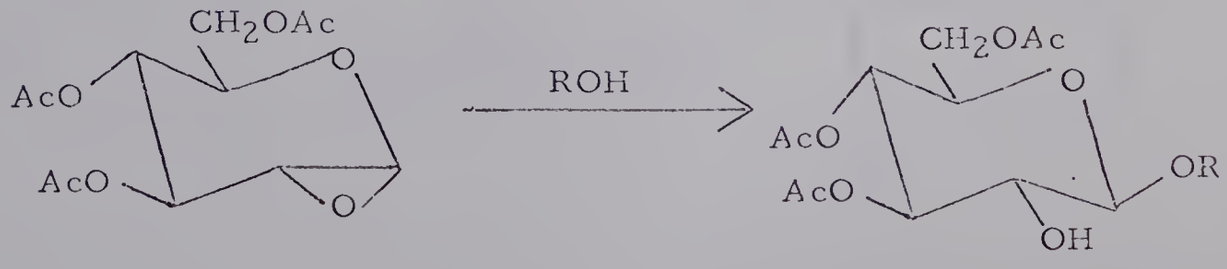


Eleven years later Lipp (12) dehydrated "acetobutyl alcohol" and obtained an anhydride to which he assigned a six-membered ring structure,



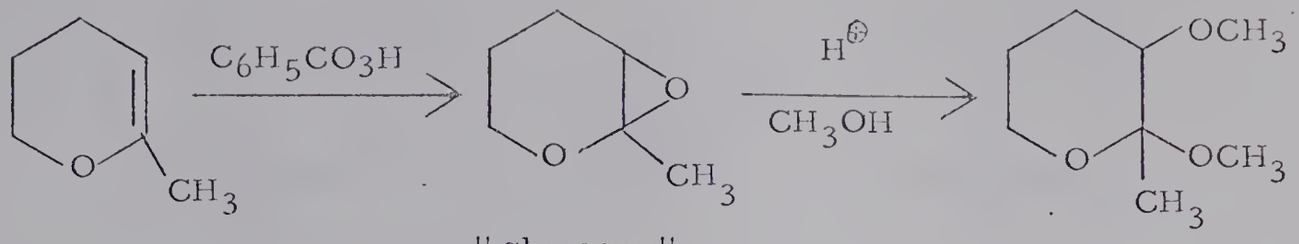
Bergmann and Miekeley (1, 2) in 1923 subjected Lipp's anhydride to oxidation by peroxybenzoic acid. They likened the oxide, which they thought had been obtained*, to the "α-glucosan" (which later

* Fried (14) in a review article on pyrans, appearing in 1950, stated that the epoxide, , described earlier (1) had actually been obtained by Bergmann in spite of Bergmann's later declaration (3) that the compound originally reported and thought to be an epoxide (1, 2) was actually a dimer of the epoxide. It is now recorded that up to the present this epoxide has not been isolated and that attempts to produce similar epoxides from 3,4-dihydro-2H-pyran (15) and other vinyl ethers (16) with peroxy acids have been unsuccessful. That epoxides of vinyl ethers are very reactive, especially in the presence of acids, is illustrated by the ready reaction of Brigl's anhydride (17) with alcohols and water.



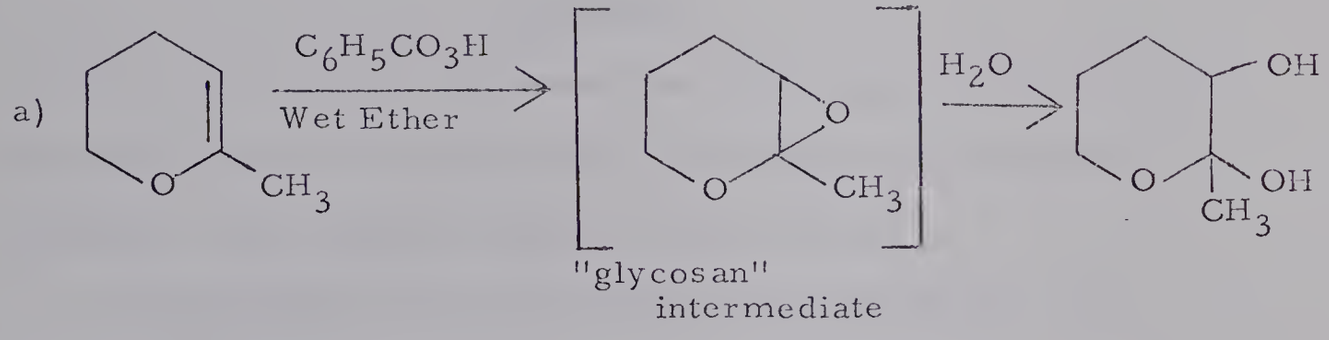
Brigl's anhydride. R = H, CH_3, C_2H_5

proved to be 1,6-anhydro-β-D-glucopyranoside) of Pictet (13).

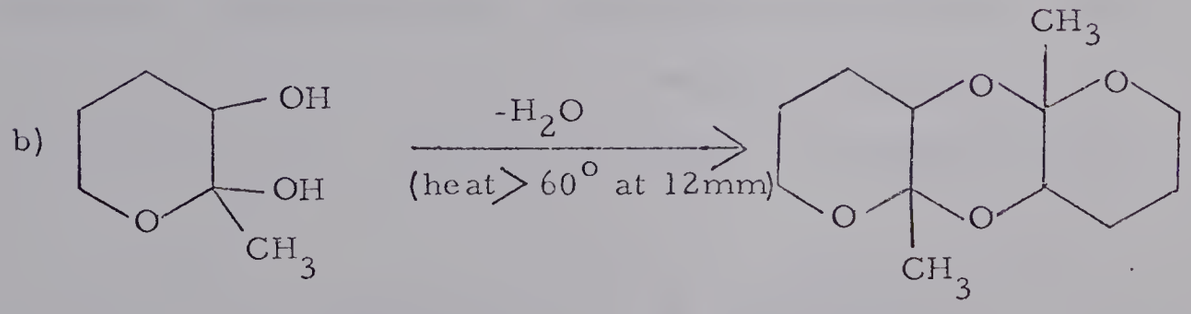


"glycosan" "glycoside"

Treatment of their "glycosan" with boiling acidic methanol gave them a "glycoside" which had chemical properties comparable to those of the carbohydrate glycosides. In a succeeding paper, in the same year they (3) reported that what had previously been said to be a glycosan was in fact a dimer of the epoxide intermediate. This they termed a "disaccharide anhydride" (Chart 1). The



"glycosan" intermediate



"disaccharide anhydride"

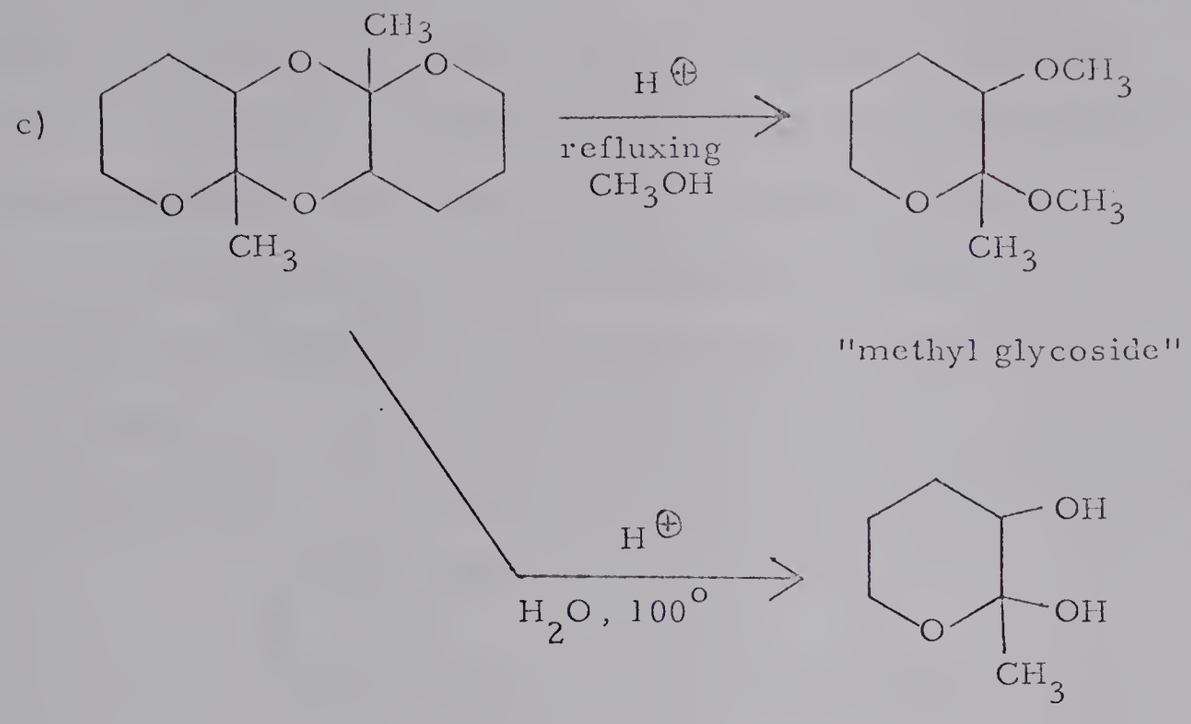


CHART 1

properties of this anhydride were later (14) compared with those of difructopyranose anhydride which, like Bergmann's anhydride, undergoes acid catalysed hydrolysis very slowly.

During this same period Helferich and Malkomes (4) prepared 5-hydroxyhexanol. When this compound was treated with acidic methanol 2-methoxy-6-methyltetrahydropyran was obtained (Chart 2). Though the aldehyde was found to reduce

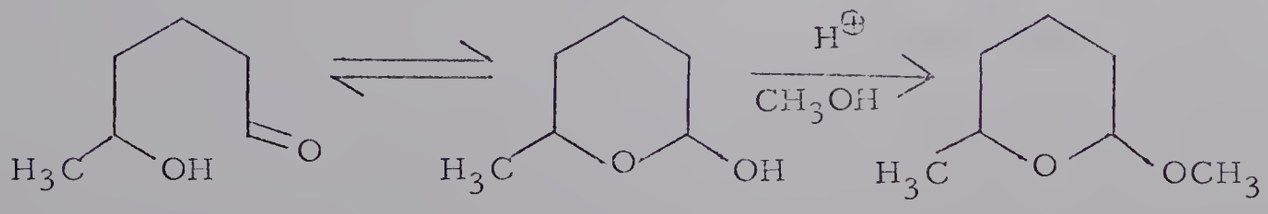
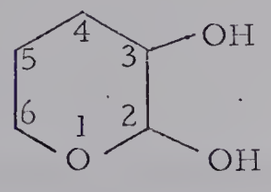


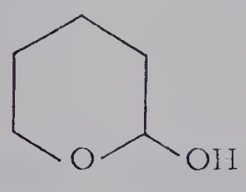
CHART 2

Fehling's solution, the methoxy compound did so barely noticeably, and in this respect the latter compound resembled a glycoside. It is interesting to note that Helferich (8) was among those who first established the pyranose ring structure for glucose.

From this point onward developments in the area of carbohydrate models went hand in hand with progress in the synthesis of substituted pyrans. Hurd and Kelso (18) found that, as in the case of carbohydrates, 2,3-dihydroxytetrahydropyran (I) turned a solution



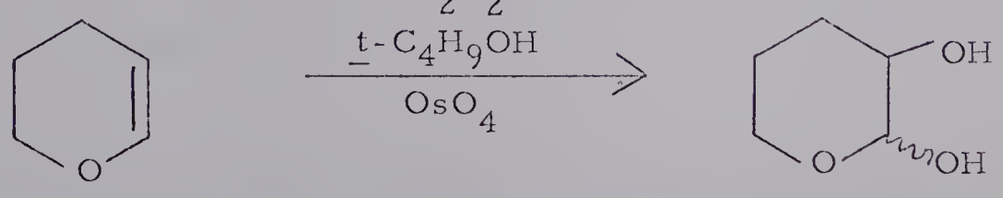
I



II

of the amino acid glycine brown ("browning reaction"). The same reaction was far less pronounced for 2-hydroxytetrahydropyran (II), which corresponded to a similar property exhibited by 2-deoxyglucose. These authors prepared the diol I by hydroxylation of 3,4-dihydro-2H-pyran, using hydrogen peroxide in t-butyl alcohol and osmium tetroxide as catalyst ((a), Chart 3).

a)



I

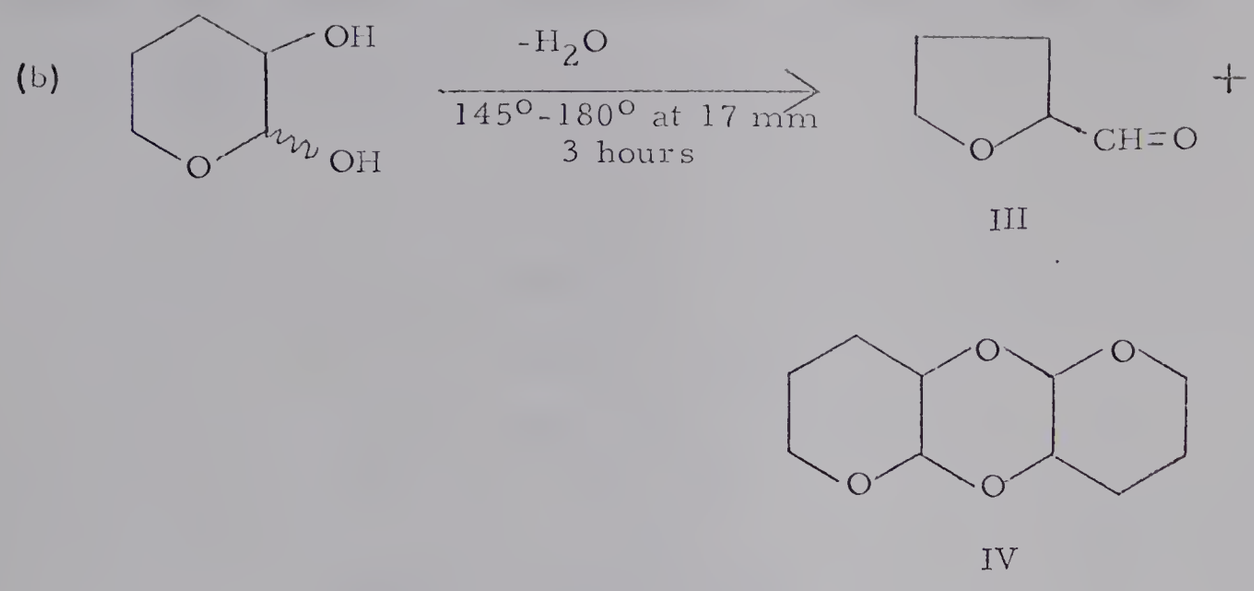
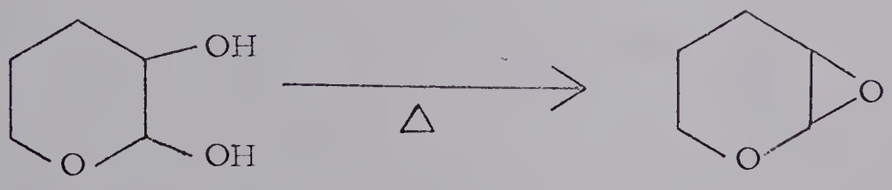


CHART 3

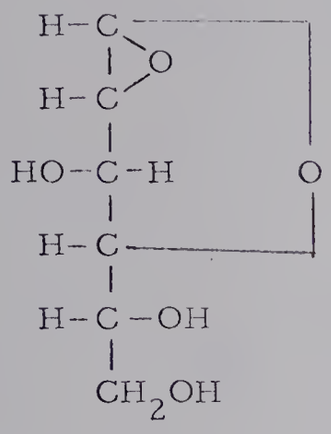
Hurd and Edwards (19) made use of the same diol (I) to study the thermal dehydration of sugars. One of the objectives of their work was to see whether an analogous compound to the α-glucosan of Pictet (13) could be obtained. If, as had been earlier suggested, α-glucosan was a 1,2-anhydro sugar it followed that 2,3-dihydroxy-tetrahydropyran, when treated under conditions similar to those used for the formation of α-glucosan, should form the 2,3-epoxide.



Of the several products obtained by Hurd and Edwards ((b), Chart 3) none was an α-glucosan analog. One product, a substance with a high melting point, was thought to be a disaccharide anhydride (IV, Chart 3), by analogy with the compound obtained by Bergmann (3).

On the basis of their work on carbohydrate models, these

authors were satisfied that the structure of Pictet's α-glucosan, accepted until then (20) as shown below,

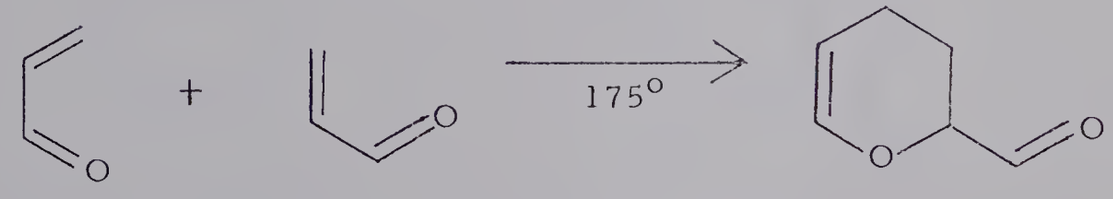


Pictet's α -glucosan (20)

required reappraisal.

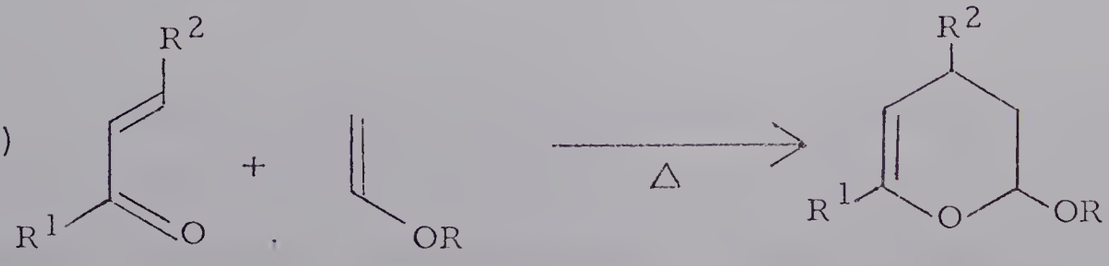
Alder and Rüden (21) in 1941 discussed the diene-like properties of acrolein and described the self-condensation of this compound to give the dimer, 3,4-dihydro-2H-pyran-2-carboxaldehyde ((a), Chart 4). Ten years later Longley and Emerson (21), and Whetstone and Ballard (22) simultaneously reported the condensation of acrolein with a variety of vinyl ethers and vinyl esters ((b), (c), and (d), Chart 4).

a)



Alder and Ruden (1941)

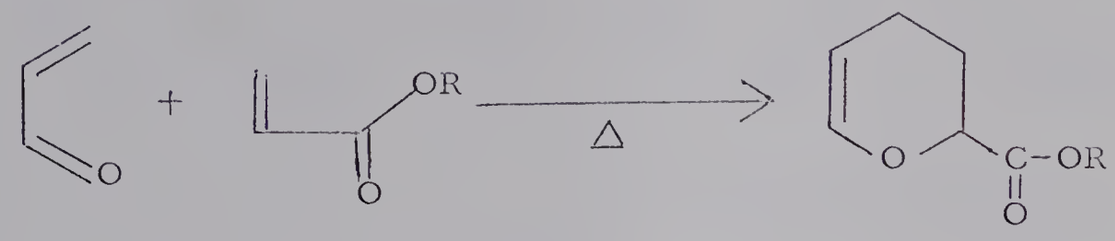
b)



Longley and Emerson (1950)

c) 

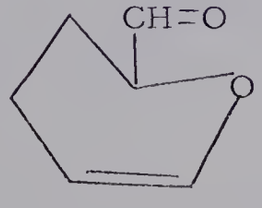
Whetstone and Ballard (1951)

d) 

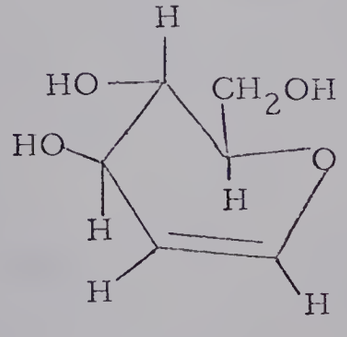
Whetstone and Ballard (1951)

CHART 4

These developments were a significant step forward, both for pyran chemistry in general, and for the preparation of carbohydrate analogs. With the "acrolein dimer", 3,4-dihydro-2H-pyran-2-carboxaldehyde, the skeletal structure of hexopyranosides was at hand.

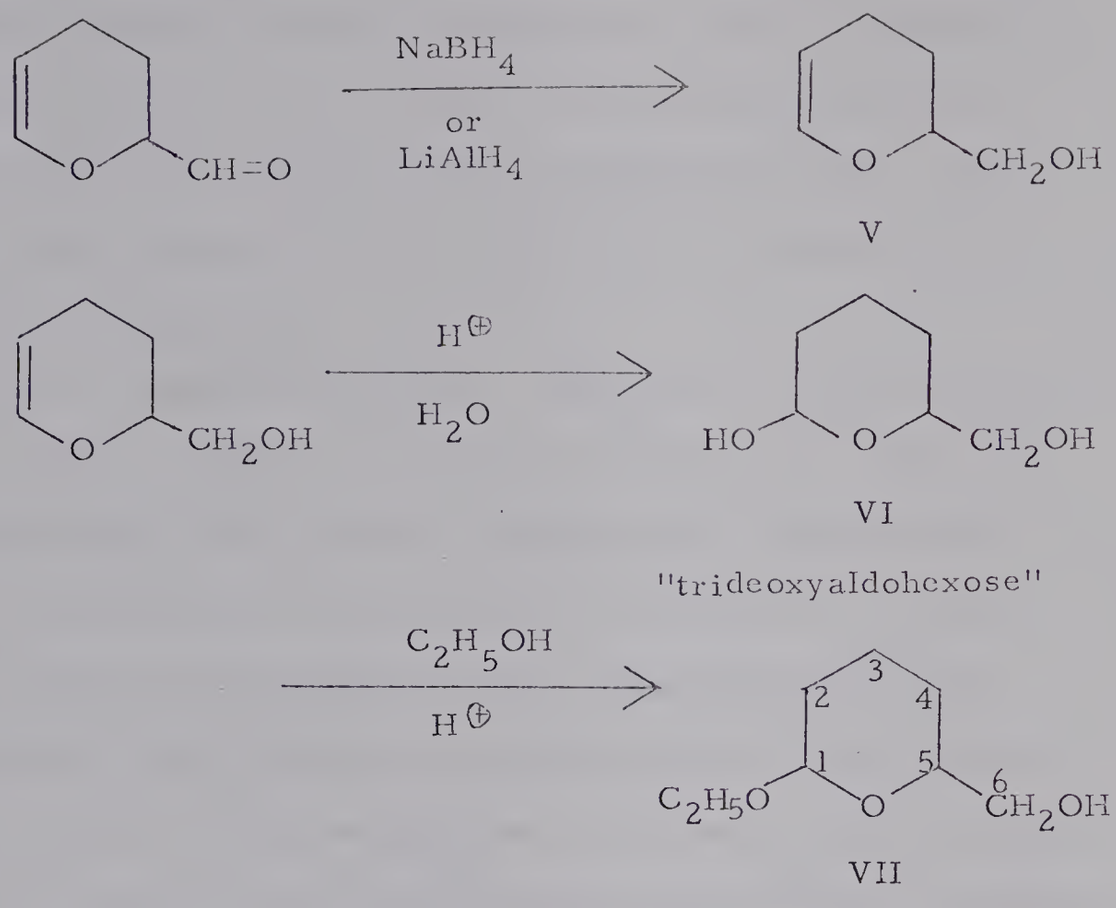


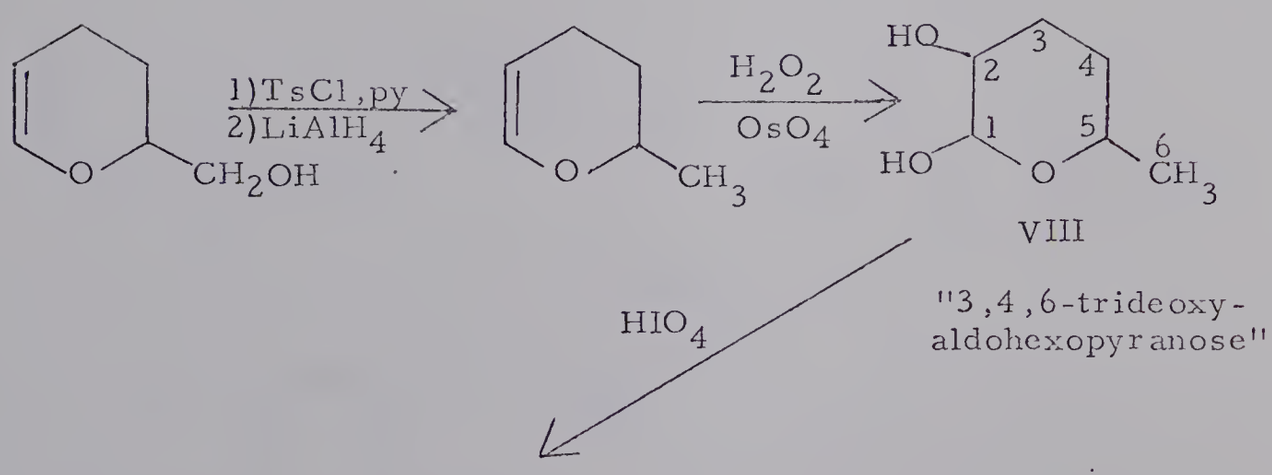
(D L) acrolein dimer



D-glucal

Zelinski et al (24, 25) reduced the acrolein dimer to the corresponding alcohol and subjected the resulting "D L-dideoxy-glucal" to hydration and hydroxylation. This gave mixtures of "polydeoxy aldohexoses" (Chart 5).





(Ts = p-CH_3-C_6H_4-SO_2-)
(py = pyridine)

CHART 5

In addition to giving a positive Fehling's test and a 2,4-dinitrophenylosazone derivative, Zelinski's 3,4,6-trideoxy aldohexopyranose (VIII, Chart 5) gave the browning reaction (25). This satisfied these authors that they had obtained a racemic mixture of polydeoxyaldohexoses.

Marchessault, Glaudemans et al (26), in 1962, prepared several substituted pyrans to serve as carbohydrate models. By studying the hydrolysis of these compounds they hoped to learn more about the factors which influence the hydrolysis of sugars. In the previous year Glaudemans (27), using the procedure of Whetstone and Ballard (23), condensed acrolein with ethyl acrylate to obtain ethyl 3,4-dihydro-2H-pyran-2-carboxylate ((d), R=C_2H_5, Chart 4). The ester was treated successively with acidic methanol then $LiAlH_4$ to give a methyl aldohexopyranoside (Chart 6), a

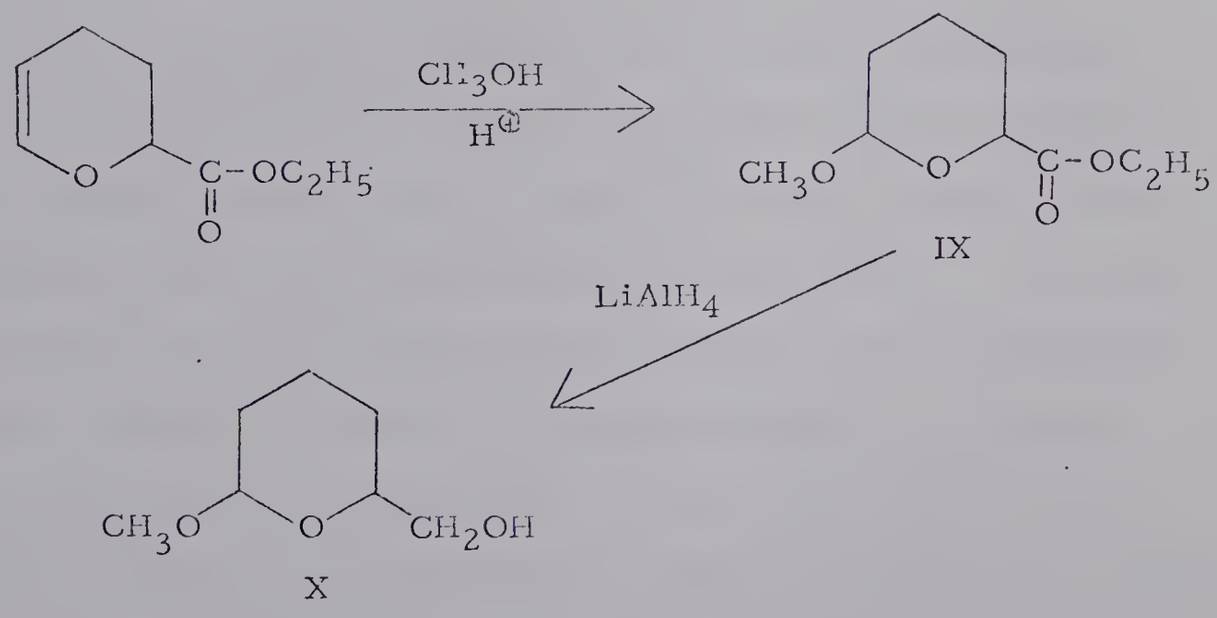
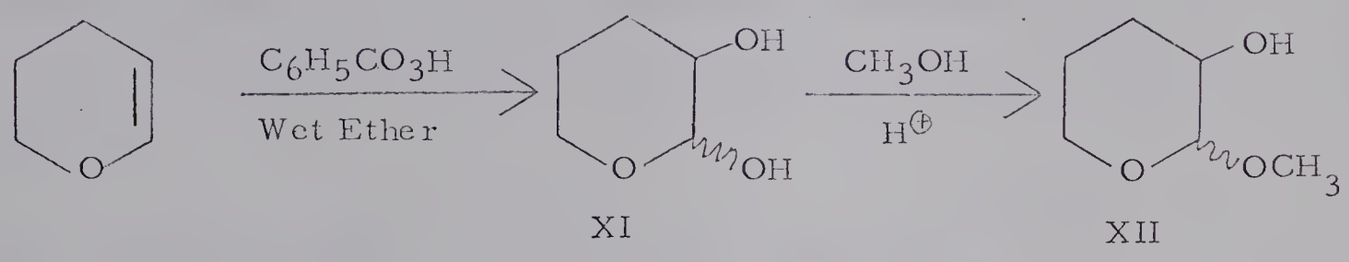


CHART 6

homolog of the compound obtained by Zelinski (25). Marchessault et al (26) prepared 2,3-dihydroxytetrahydropyran by treating

3,4-dihydro-2H-pyran with peroxybenzoic acid in wet ether. The diol was heated with acidic methanol to give a cis, trans mixture of 3-hydroxy-2-methoxytetrahydropyran (Chart 7).



XI XII

CHART 7

These workers subjected all of the above carbohydrate models (IX, X, Chart 6 and XII, Chart 7) along with 2-methoxytetrahydropyran, and certain pyranosides, to acid hydrolysis. The results that emerged from the kinetic studies of the hydrolysis of these compounds was revealing. Comparison of the rate constants obtained for the 2,6-disubstituted tetrahydropyrans showed a progressive decrease in rates of hydrolysis when the substituent at the 6-position was respectively H, CH_2OH, CO_2H and $CO_2C_2H_5$, and a methoxy group was at position 2 in all cases. Also a corresponding decrease was found in the rate of hydrolysis of 2-methoxytetrahydropyran as compared with 3-hydroxy-2-methoxytetrahydropyran, and methyl 2-deoxy-α-D-glucopyranoside as compared with methyl-α-D-glucopyranoside. These results permitted the authors to derive a semiquantitative conclusion concerning the effects of variation in the electronegativity of groups at various positions on the pyran ring, on the rate of hydrolysis of glycopyranosides. This work demonstrated the extent to which carbohydrate models could be

useful in leading to an understanding of the chemistry of sugars.

Further developments in the synthesis of substituted pyrans came with the procedure reported by Alder et al (28). By condensing cis- or trans-1-acetoxy-2-ethoxyethylene with acrolein the cis- or trans-2-acetoxy-3-ethoxy-2,3-dihydropyran was obtained ((c), Chart 8).

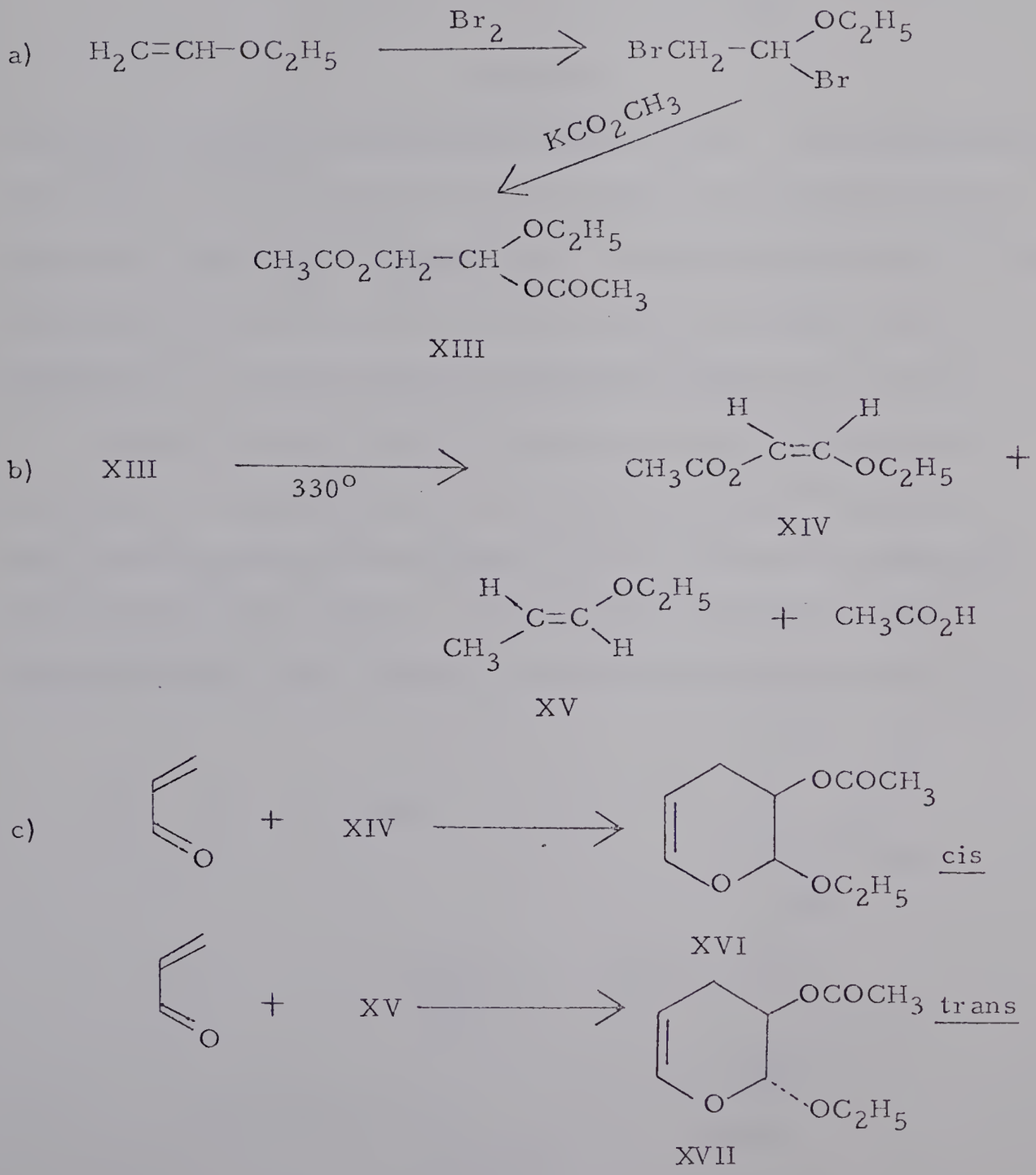


CHART 8

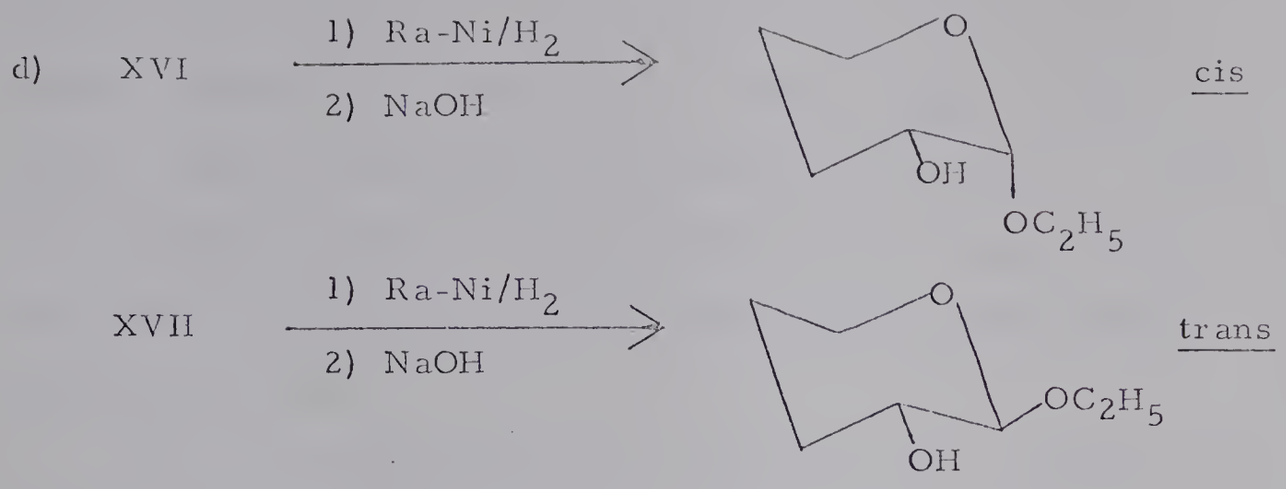


CHART 8

The cis-(or trans-)2,3-disubstituted dihydropyran was hydrogenated, then saponified to give cis-(or trans-)2-ethoxy-3-hydroxytetrahydropyran ((d), Chart 8). Though the net result of this synthesis was the stereoselective production of one of two possible isomeric tetrahydropyrans, the route leading to the final product was a long one.

More recently, while the work described in this thesis was in progress, a preparation of 2,3-disubstituted tetrahydropyrans, more convenient than that of Alder (28), was reported by Bakassian and Descotes (29), in 1966. These workers obtained 3-chloro-2-hydroxytetrahydropyran (XVIII, Chart 9) by adding hypochlorous acid

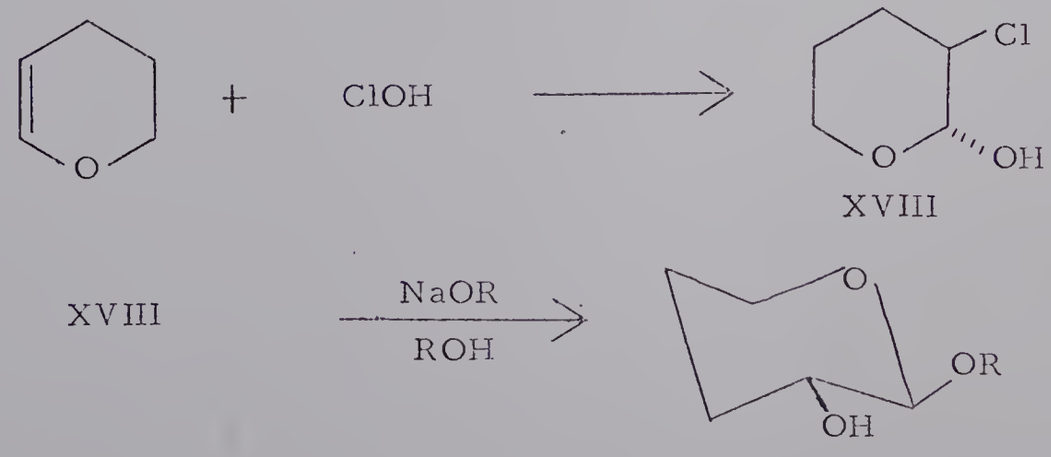
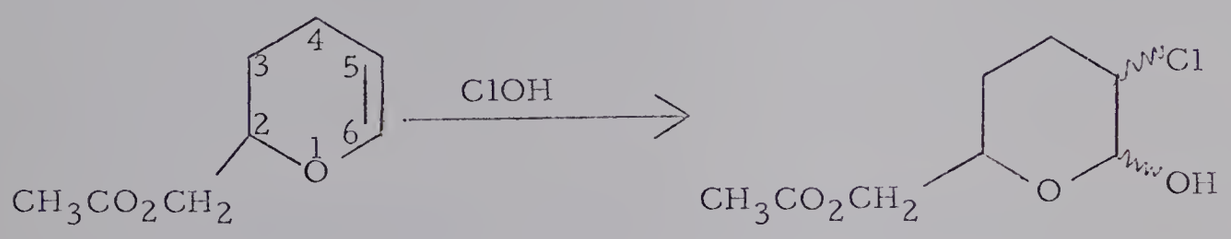


CHART 9

to 3,4-dihydro-2H-pyran. By treating the chlorohydrin XVIII with hot alkaline alcohol these authors obtained trans-2-alkoxy- or trans-2-aryloxy-3-hydroxytetrahydropyrans (XIX, Chart 9). This stereoselective synthesis of trans products was an improvement over Alder's method since only two steps were required to obtain the desired product.

In a succeeding publication, in the same year, Aguilera and Descotes (30) described the addition of hypochlorous acid to 2-acetoxymethyl-3,4-dihydro-2H-pyran,



Isomeric Mixture

These authors were mainly interested in the isomer distribution of the resultant chlorohydrins. However, extension of this reaction to the synthesis of polydeoxyaldohexopyranosides is clear.

RESULTS AND DISCUSSION

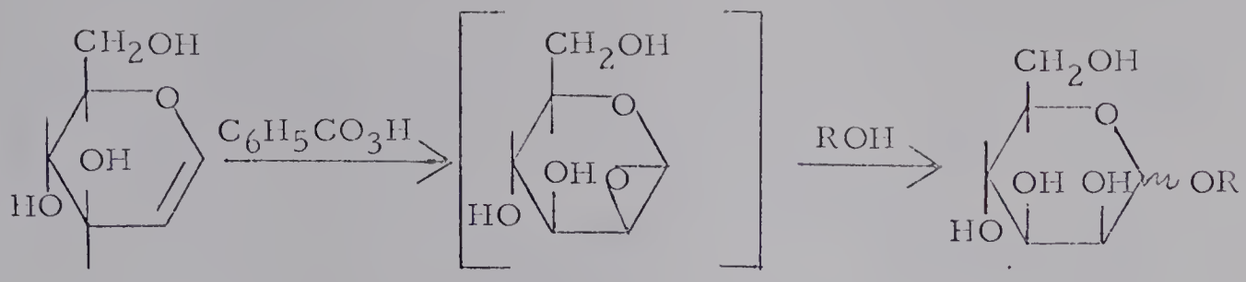
I. INTRODUCTION OF OXYGEN AT THE 2- AND 3-POSITIONS ON THE TETRAHYDROPYRAN RING.

In the Introduction to this thesis it was pointed out that preparations are known which lead to tetrahydropyrans bearing oxygen-substituents at the 2- and 3-positions. However, each method has its disadvantages. In one procedure (28) where molecules of definite structure are obtained, the synthesis requires many steps. An alternative, and simpler, route (26) to 2,3-disubstituted tetrahydropyrans produces a mixture of cis- and trans-isomers which cannot be separated by fractional distillation.

As part of one of the objectives of the present work, a simple, productive and stereospecific preparation of 2,3-disubstituted tetrahydropyrans was developed, which is now discussed.

A. Preparation and structure of 2-alkoxy-3-hydroxytetrahydropyrans, and 2,3-dialkoxytetrahydropyrans.

Glycals (31), which are α,β-unsaturated pyranyl ethers, have in a number of cases been oxidized by peroxybenzoic acid to give, first, what is believed to be an epoxide intermediate. Under the reaction conditions this was rapidly converted into either a reducing sugar or a glycoside in the presence of water, alcohols or a carboxylic acid (3, 31, 32, 33) as shown in Chart 10.

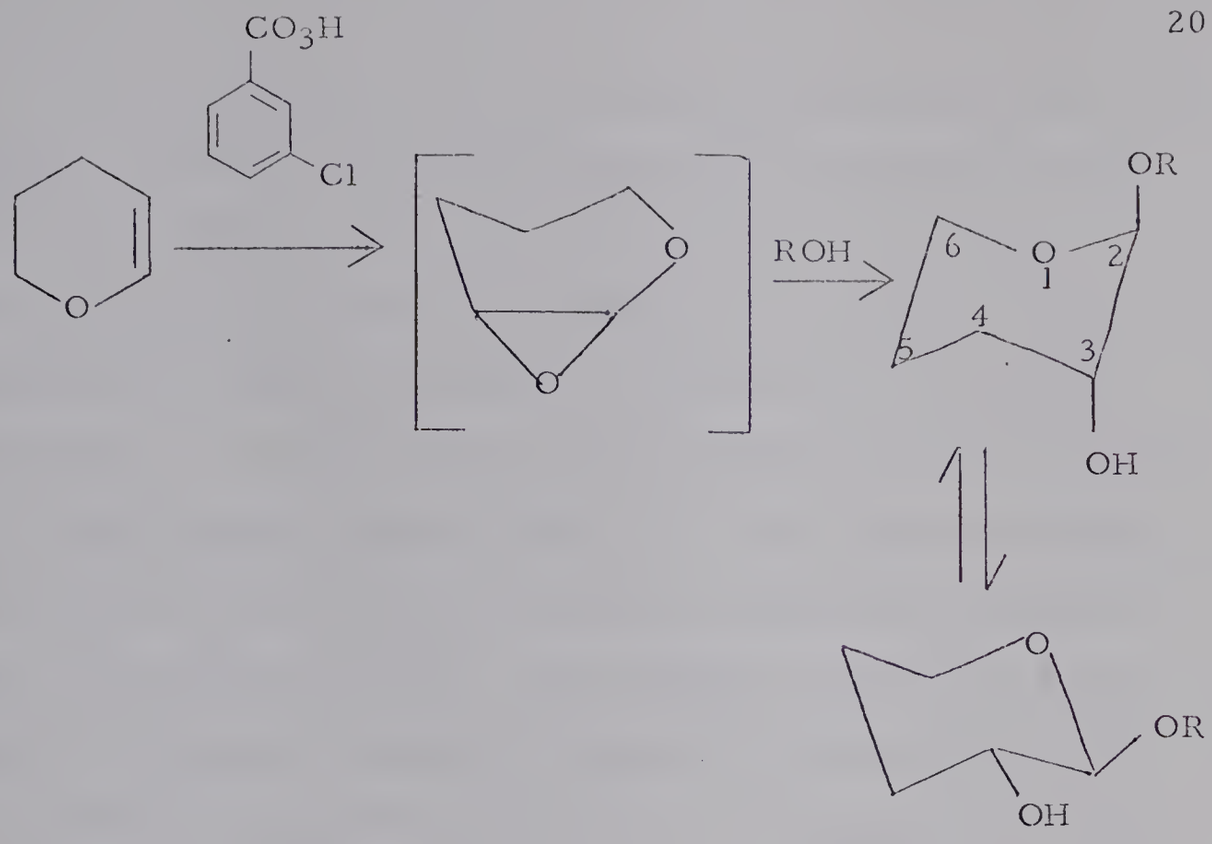


R = H, alkyl, benzoyl

CHART 10

In a similar reaction Bergmann et al (3) (previously discussed on page 5) showed that oxidation of 6-methyl-3,4-dihydro-2H-pyran by peroxybenzoic acid in wet ether provided the diol, 2-methyl-2,3-dihydroxytetrahydropyran. More recently (34) 3,4-dihydro-2H-pyran was similarly oxidized to 2,3-dihydroxytetrahydropyran. When the olefin was treated with peroxybenzoic acid in anhydrous ether, only 2-benzoyloxy-3-hydroxytetrahydropyran was obtained (34). A trans configuration was tentatively assigned to this product on the basis that an epoxide intermediate was considered to be formed as the precursor during the reaction.

Using the work mentioned above as a basis the present investigations provided a simple and more productive route to 2-alkoxy-3-hydroxytetrahydropyrans. These compounds were obtained by using either peroxybenzoic acid or m-chloroperoxybenzoic acid to oxidize 3,4-dihydro-2H-pyran dissolved in the appropriate alcohol, as shown in Chart II*.



R = CH_3, C_2H_5, i-C_3H_7, t-C_4H_9.

CHART 11

Analysis by gas liquid chromatography showed the isolated product to consist of two components in the approximate ratio of 95:5. Elemental analysis of this mixture agreed with the structures for cis- and trans-3-hydroxy-2-alkoxytetrahydropyran . Furthermore, the boiling point and refractive index of this product were closely similar to those reported by Marchessault, et al (26), who prepared this compound by a different route (Chart 7, p. 13).

* At about the same time as the work in this thesis was reported (F. Sweet and R. K. Brown. Can. J. Chem. 44, 1571 (1966)) a publication appeared by Bakassian and Descotes (29) in which the preparations of several 2-alkoxy and 2-aryloxy-3-hydroxy-tetrahydropyrans are described. The work by these authors has been discussed on page 15.

The major component in the product mixture was found to be trans-3-hydroxy-2-methoxytetrahydropyran on the basis of the following evidence. The nuclear magnetic resonance (n.m.r.) spectrum in $CDCl_3$ of the 95:5 mixture, showed signals for the anomeric C-2 proton as doublets at τ 5.80 ($J_{2,3}$ = 5.2 Hz) and τ5.43 ($J_{2,3}$ = 3.2 Hz) where the signal at higher field represented the major isomeric component (Fig. 1). Each isomer can exist in two different conformations that are in equilibrium with each other ((a) and (b), Chart 12). The coupling constant of 3.2 Hz agrees with the axial-equatorial relation (35, 36) of the C-2 and C-3 protons found for both conformations of the cis isomer ((a), Chart 12). The trans isomer, however, requires the C-2 and C-3 protons to be in either a diaxial or diequatorial arrangement.

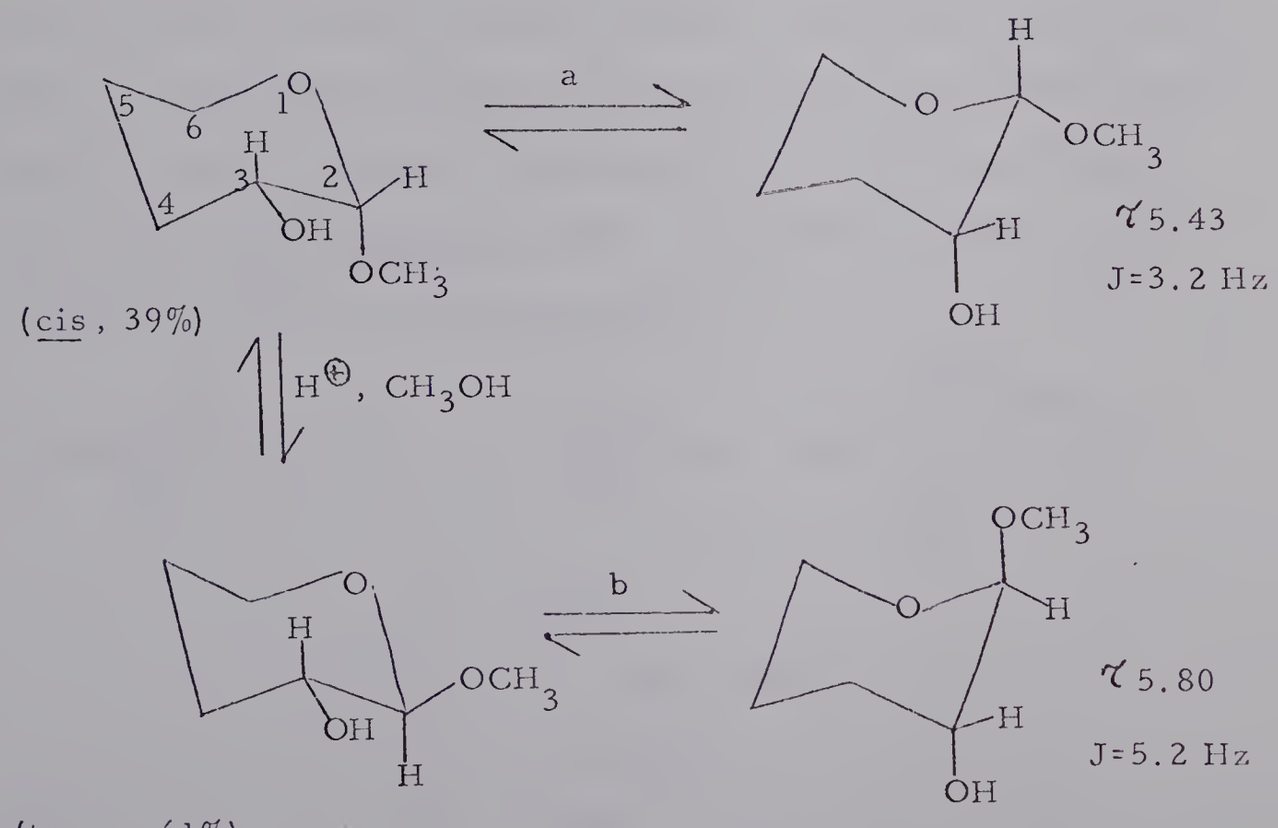
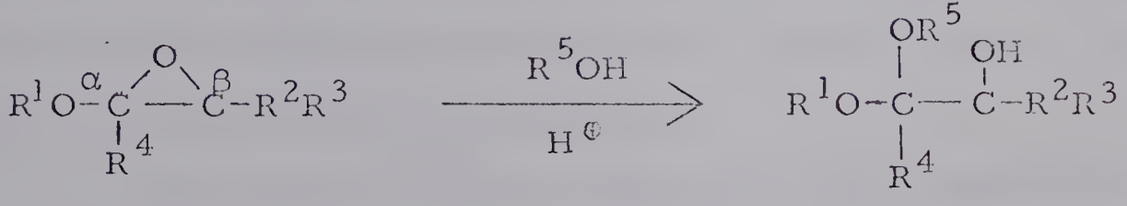


CHART 12

In the H-2 , H-3 diequatorial conformation the coupling ($J_{2,3}$) between the two protons is expected to have a value similar to that for the axial-equatorial case (35, 36). On the other hand in the H-2, H-3 trans-diaxial conformation $J_{2,3}$ is expected to be much larger, in the range of 7-9 Hz (35, 36). The observed value of 5.3 Hz is in agreement with a time-averaged signal obtained from both conformations of the trans isomer (35, 36). On a similar basis Lemieux and Fraser-Reid (37) assigned configurations to cis- and trans-3-bromo-2-methoxytetrahydropyran. Here also the higher field doublet with the larger spacing, for the C-2 proton, was assigned to the trans isomer.

The proposal of initial formation of an intermediate epoxide (Charts 10 and 11) is supported by the fact that the reaction product is almost exclusively the trans-2-alkoxy-3-hydroxytetrahydropyran. This is in agreement with the known preferred trans opening of the epoxide ring (16), and also the observation (16) that epoxides of vinyl ethers open exclusively at the α-position in acidic alcohol (Chart 13), to give α-hydroxy acetals.



R^1 = alkyl

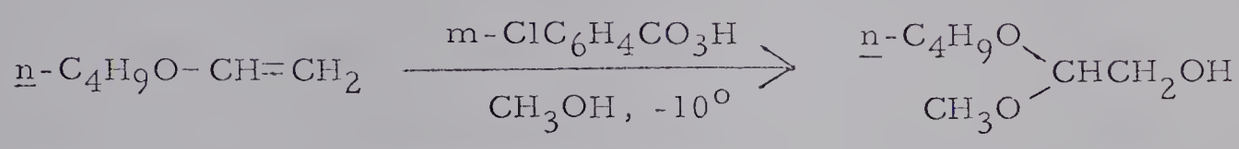
R^2, R^3 = H, alkyl, phenyl

R^4 = H, phenyl

R^5 = alkyl

CHART 13

When a methanolic solution of n-butyl vinyl ether was treated in this laboratory with m-chloroperoxybenzoic acid, under the same conditions as were used to prepare trans-3-hydroxy-2-methoxytetrahydropyran and its homologs, a 92% yield was obtained of the known (38) compound, n-butyl-β-hydroxy-α-methoxyethyl ether. This



provides further evidence for an epoxide intermediate (Chart 13) in these reactions as well as support for the configurational assignment for the C-3 OH and C-2 OCH_3 groups in the disubstituted tetrahydropyran obtained under these conditions.

Attempts to isolate the epoxide intermediate resulting from treatment of 3,4-dihydro-2H-pyran with peroxybenzoic acid were unsuccessful. This is not surprising in view of the fact that attempts by other workers (3, 15, 34) to isolate this epoxide intermediate, generated under similar conditions, consistently met with failure. However, to account for the product obtained in this reaction, either such an intermediate must be formed or, alternatively, an "epoxide-like" transition state must be involved.

If the reaction mixture, obtained from the epoxidation in alcohol of the α,β-unsaturated cyclic ether, was worked up immediately after completion of the reaction, gas liquid chromatography (g.l.c.) showed that the trans isomer obtained was contaminated by less than 1% of the cis isomer. If the reaction mixture stood for 2 days

at room temperature before work-up, the amount of cis contaminant increased to about 5-10%. This showed that isomerization had taken place, no doubt caused by the presence of benzoic acid (or m-chlorobenzoic acid).

When 3-hydroxy-2-methoxytetrahydropyran was treated with acidic (p-toluenesulfonic acid) methanol an equilibrium mixture (39:61) of cis and trans isomers was obtained (Chart 12). These isomers could be readily separated by preparative g.l.c.. The same proportion of cis and trans isomers was found when either the pure cis or pure trans isomer was equilibrated under the same conditions.

The hydroxyl function of the 2-alkoxy-3-hydroxytetrahydropyrans could be readily alkylated or benzoylated (Chart 14).

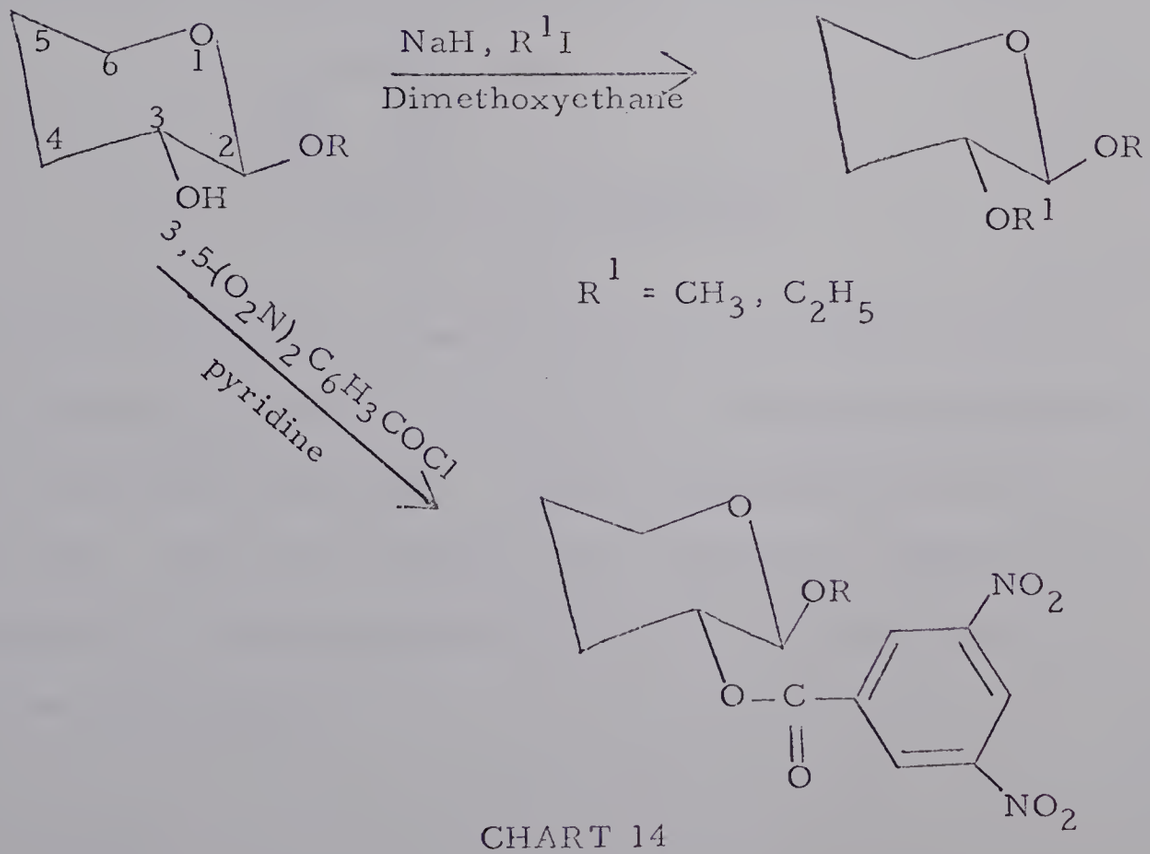
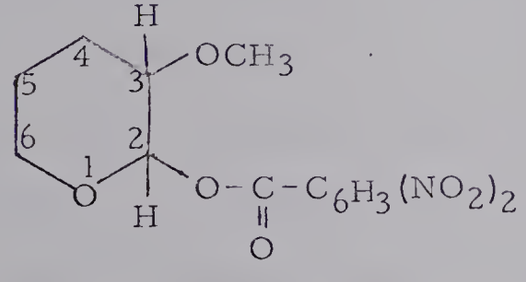


CHART 14

The 3,5-dinitrobenzoate derivatives (solids) were useful in characterizing the 3-hydroxy compounds. The n.m.r. spectra of these derivatives proved to be of some value in gaining additional evidence for the structures assigned to these molecules. Compared to the C-3 proton signal position in the corresponding 3-hydroxy compound (τ 6.0-6.5) (which is obscured by other CH-O absorptions) the position for the C-3 proton absorption in the corresponding 3,5-dinitrobenzoate occurs at much lower field (τ 5.0) and therefore is clearly visible. There is an attendant slight downfield shift (ca. 0.3 ppm) of the anomeric proton signal accompanied by a narrowing in the spacing for the doublet ($J_{2,3}$). This shows that the hydroxyl group and the alkoxy group are on adjacent carbons in the precursor. Also the OH group must be on carbon 3 and the alkoxy group on carbon 2. If the reverse were true, a large

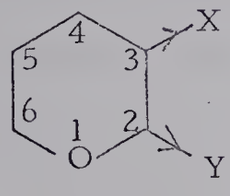


downfield shift would be expected for the H-2 doublet in the 3,5-dinitrobenzoate derivative. Also, the H-3 multiplet would undergo only a small downfield shift. However, the opposite of this is observed. Thus the C-2 alkoxy and C-3 hydroxyl configurational assignment for these compounds (Chart 11) is further supported by these observations.

B. Conformational preference of 2,3-disubstituted tetrahydropyrans.

1. Models to obtain spin-spin couplings for the anomeric proton of 2,3-disubstituted tetrahydropyrans.

It is well known that the magnitudes of coupling constants, as well as of chemical shifts, are dependent to some extent upon the electronic environment about C-2 and C-3. Electronegative



atoms connected to C-2 and C-3 of these six-membered ring systems reduce the coupling constants (39, 40, 41, 42) and also cause a marked downfield shift of the resonance signals for the C-2 and C-3 protons (43, 44). Thus, if we wish to use the magnitude of the couplings or the extent of chemical shift to estimate the proportion of conformers present in 2,3-dialkoxytetrahydropyrans, it is imperative that a model be chosen which resembles these compounds as closely as possible. In particular carbons 2 and 3 in the model compound should have the same atoms on them as in the disubstituted tetrahydropyrans, which they represent. Also, these models should possess the necessary rigid conformational forms. These would provide the H-2, H-3 proton couplings required for such calculations.

Up to the time of the present work, the only models available which approximate these desirable features are those from the field

of carbohydrate chemistry. A number of fully acetylated glycopyranosides are considered to be conformationally fixed, giving coupling constants of 5-8 Hz for the H-1, H-2* trans-diaxial protons and 2.0-3.2 for the H-1, H-2 equatorial-axial protons (41). The possibility exists, however, that some twisting occurs in these acetylated carbohydrate molecules which would affect the magnitude of the coupling of the vicinal hydrogen atoms (42, 45).

To provide such optimum models both cis and trans-tetrahydropyrano[2,3-b]-1,4-dioxane were prepared, by the reaction sequence shown in Chart 15.

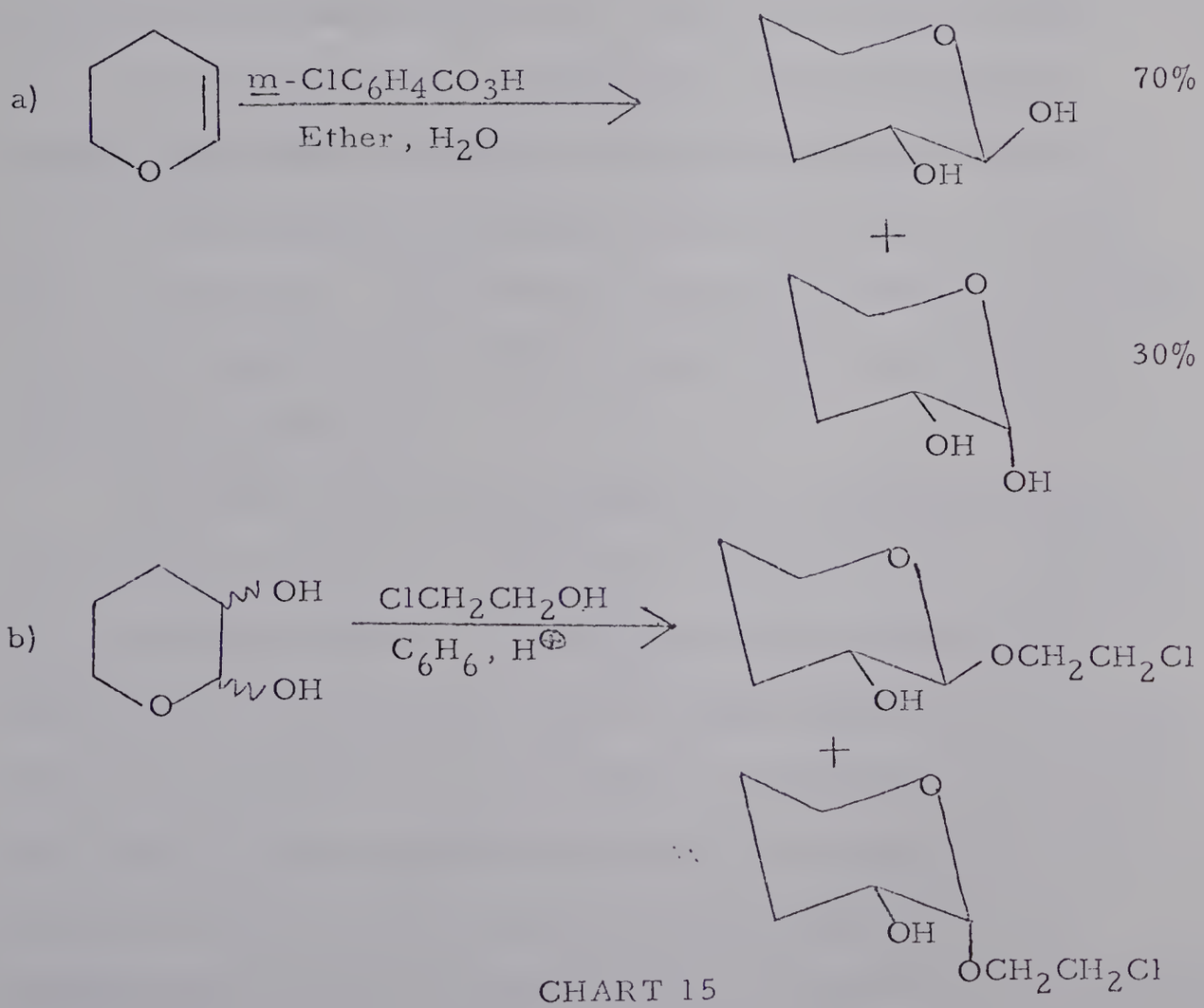
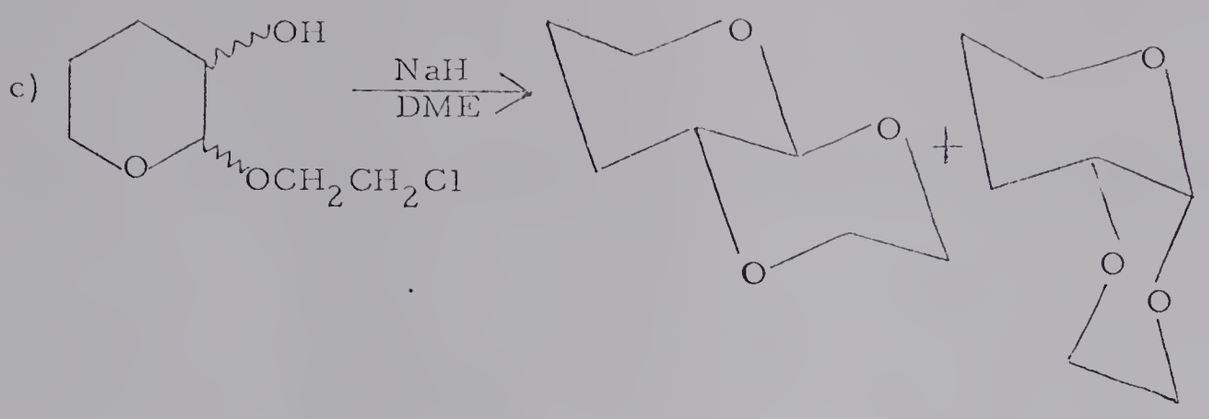


CHART 15

* C-1 and C-2 in carbohydrate nomenclature is analogous to C-2 and C-3 in the pyran system.



DME = Dimethoxyethane

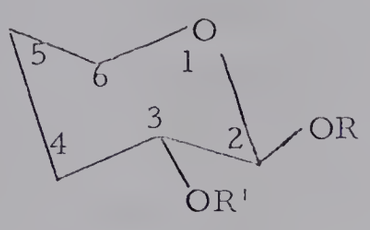
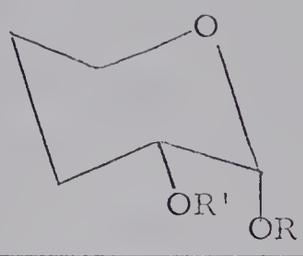
CHART 15

The procedure of Barker et al (34) was used to prepare 2,3-dihydroxytetrahydropyran ((a), Chart 15) using m-chloroperoxybenzoic acid as the oxidizing agent. When the aqueous solution of the diol was extracted with ether and then freed from water by fractional distillation under reduced pressure, a "crude diol" was obtained. This could be used without further purification in the next step ((b), Chart 15) to produce 2-(β-chloroethoxy)-3-hydroxytetrahydropyran.

The n.m.r. spectrum (60 MHz) of the crude diol (Table 1) indicated it to be a mixture of the cis and trans isomers. In $CDCl_3$ the signal for the anomeric (C-2) proton for one of the isomers occurred at τ 5.05 (doublet, $J_{2,3}$ = 2.5 Hz) while that for the other was at τ 5.53 (doublet, $J_{2,3}$ = 6.5 Hz). The signal at higher field and with the larger coupling was assigned to the trans isomer for the same reasons as those advanced for the assignment of the configurations of cis and trans-3-hydroxy-2-methoxytetrahydropyrans, already discussed at length in the preceeding section (pages 21-22).

TABLE I

N.m.r. Data for cis- and trans-2,3-Disubstituted tetrahydropyrans.[a]

trans  ;  cis

	Substituent		Chemical Shift	Coupling Constant
	R	R'	τ C-2 H	$J_{2,3}$ Hz
trans-isomer	H	H	5.42[b]	6.5[b]
			5.53[c]	6.5[c]
	CH_2CH_2Cl	H	5.71[c]	5.0[c]
	CH_2	CH_2	5.84[c,d]	7.1[c,d]
cis-isomer	H	H	4.99[b]	2.5[b]
			5.05[c]	2.5[c]
	CH_2CH_2Cl	H	5.31[c]	3.2[c]
	CH_2	CH_2	5.49[c,d]	1.3[c,d]

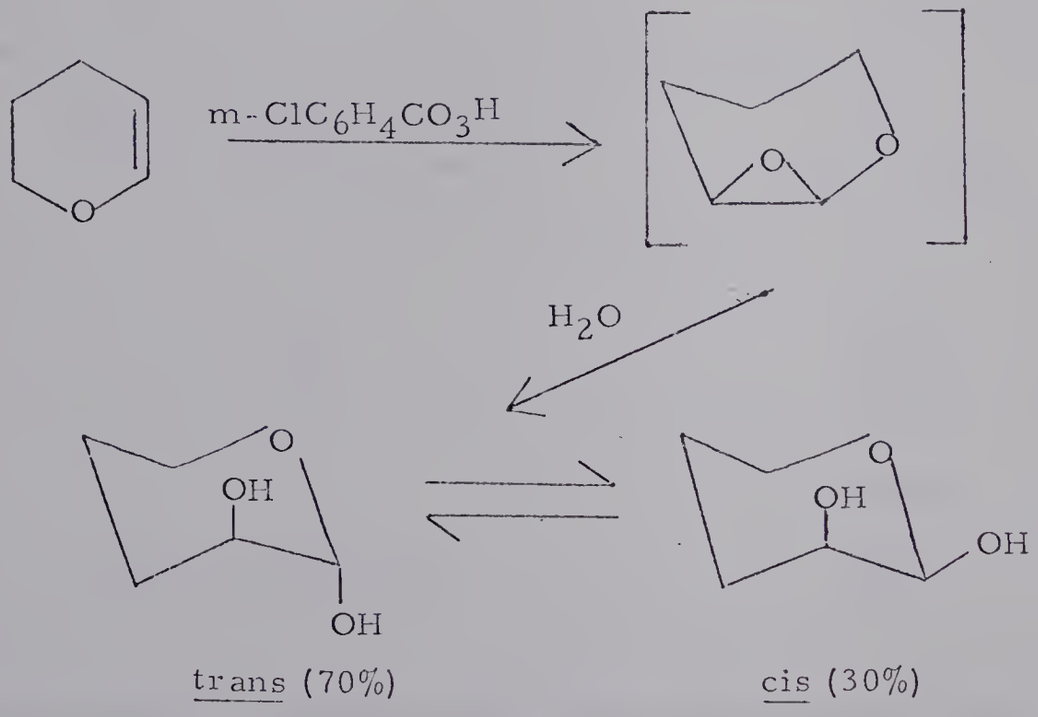
[a] Obtained on a Varian A-60, 60 MHz N.m.r. Spectrometer; tetramethylsilane as reference.

[b] In D_2O solution.

[c] In $CDCl_3$ solution.

[d] Same as values obtained on a 100 MHz spectrometer.

Integration of the n.m.r. spectrum showed that the ratio of cis to trans diol was 30:70 ((a), Chart 15). This was the ratio found when the reaction mixture was treated with water and worked up, to obtain the diol, within one hour after the reaction with peroxy acid was complete (see Experimental part). The same ratio of isomers was obtained when the crude diol mixture was allowed to equilibrate in the presence of a small amount of p-toluene-sulfonic acid. It is clear that if the reaction of 3,4-dihydro-2H-pyran with the peroxy acid had taken place to give an epoxide intermediate, on subsequent reaction with water the trans-diol must have been produced initially. Then a rapid isomerization must have occurred to form the observed equilibrium mixture.



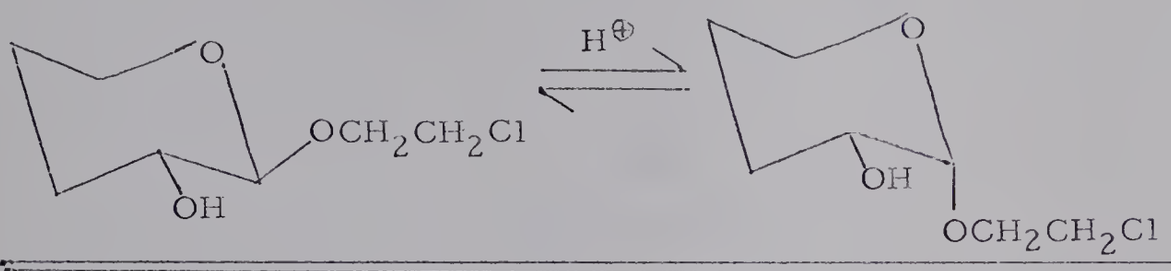
trans (70%) cis (30%)

The second step of the synthesis ((b), Chart 15) involved the acid catalysed reaction of the crude diol with β-chloroethanol in benzene. This produced a cis and trans- mixture of 2-(β-chloro-ethoxy)-3-hydroxytetrahydropyran in 53% yield. Analysis by gas-

liquid chromatography and comparison of the integrated areas for the two II-2 signals in the n.m.r. spectrum showed the cis and trans isomers to be present in the ratio of 69:31, respectively (Table II). When this mixture of isomers was allowed to equilibrate in β-chloroethanol containing a small amount of p-toluenesulfonic acid the cis to trans ratio changed to 40:60 (Table II). This indicates that the

TABLE II

Equilibration data for 2-(β-chloroethoxyl)-3-hydroytetrahydropyran.



Time of Equilibration (hours) (at room temperature)	Ratio of cis to trans
0	69:31
24	45:55
48	40:60
72	40:60
1 hour heating at 60°	40:60

initial reaction of the diol with β-chloroethanol ((b), Chart 15) is stereospecific. The cause of this stereospecificity is not certain. It could arise from and S_N2 displacement of the protonated C-2 hydroxyl group of the diol giving by Walden inversion, 2-(β-chloroethoxy)-3-hydroxytetrahydropyran as the observed mixture (cis:trans

= 69:31) ((a) pathway B , Chart 16).

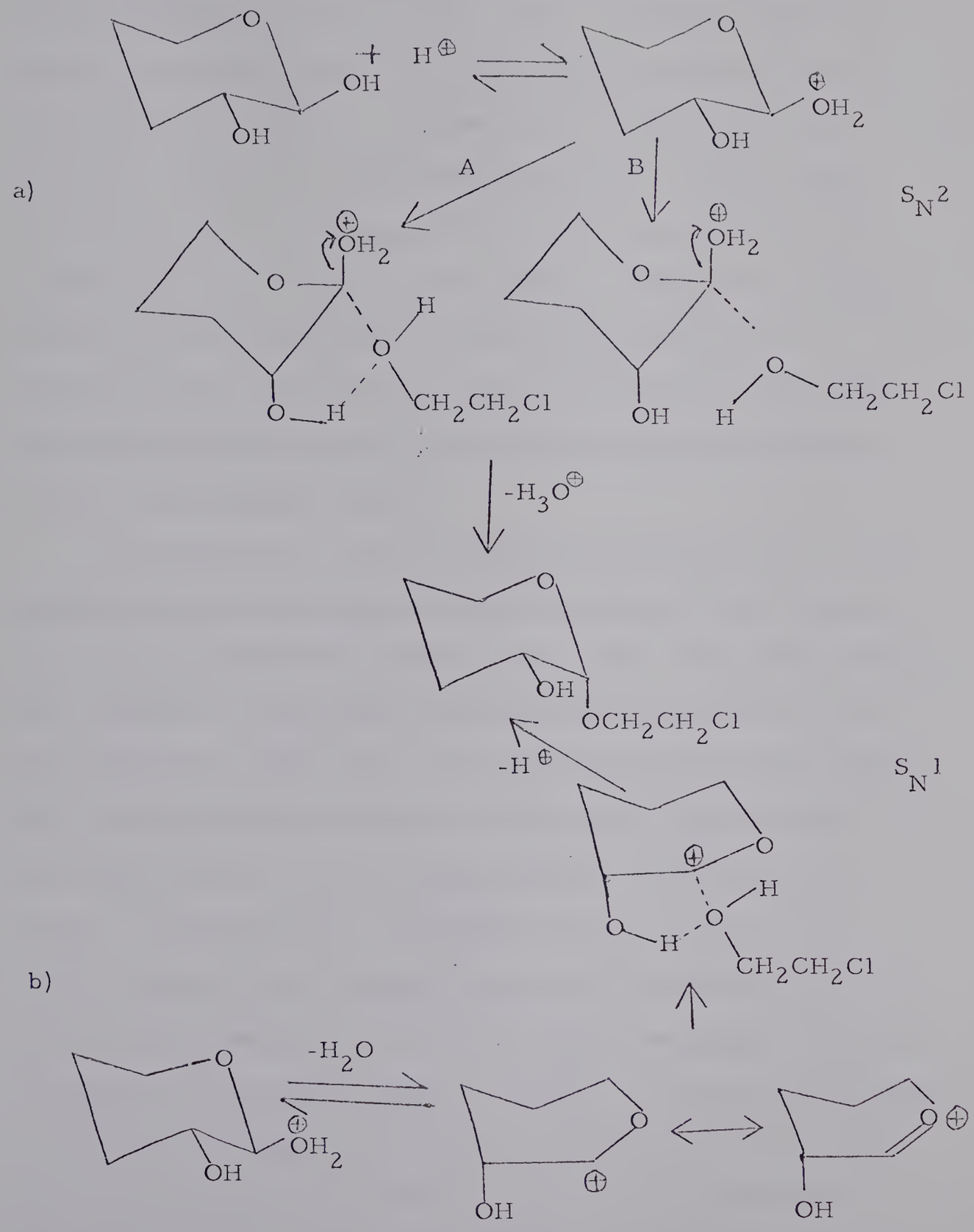


CHART 16

A second possibility involves hydrogen bonding by the C-3 hydroxyl with the incoming alcohol, giving a marked preference for attack by β-chloroethanol (via an S_N2 or S_N1 mechanism) on the same side of the ring as is occupied by the C-3 hydroxyl group ((a) or (b), Chart 16). Subsequent partial isomerization would lead to the ratio of cis to trans (69:31) actually obtained under the reaction conditions. Such directive effects arising from hydrogen bonding have been postulated to explain the preponderance of epoxidation cis to the hydroxyl group in cyclohexene-3-ol (46, 47) and of preferential addition of methylene cis to the hydroxyl group in 4-hydroxycyclopentene (48).

A crude mixture of cis and trans-tetrahydropyrano [2,3-b] - 1,4-dioxane was obtained from 2-(β-chloroethoxy)-3-hydroxytetra-hydropyran by addition of a solution of the latter compound in dimethoxy-ethane (DME) to a suspension of sodium hydride in DME at room temperature ((c), Chart 16). Fractional distillation of the product under reduced pressure afforded, in 88% yield, a solid isomer (b.p. 65° at 5 mm; m.p. 64°) and a liquid isomer (b.p. 80° at 20 mm). Configurational assignments for these isomers were readily made by n.m.r. using the spacing of the doublets due to the anomeric (H-2) protons, as was done for cis- and trans-3-hydroxy-2-methoxytetrahydropyran (pages 21 and 22). The solid (trans) isomer in $CDCl_3$ shows a signal for H-2 at τ 5.84 ($J_{2,3}$ = 7.1 Hz) while for the liquid (cis) isomer the H-2 signal occurs as a doublet at τ 5.49 ($J_{2,3}$ = 1.3 Hz) in their expanded 100 MHz spectra (Figs. 2 and 3, and Chart 17).

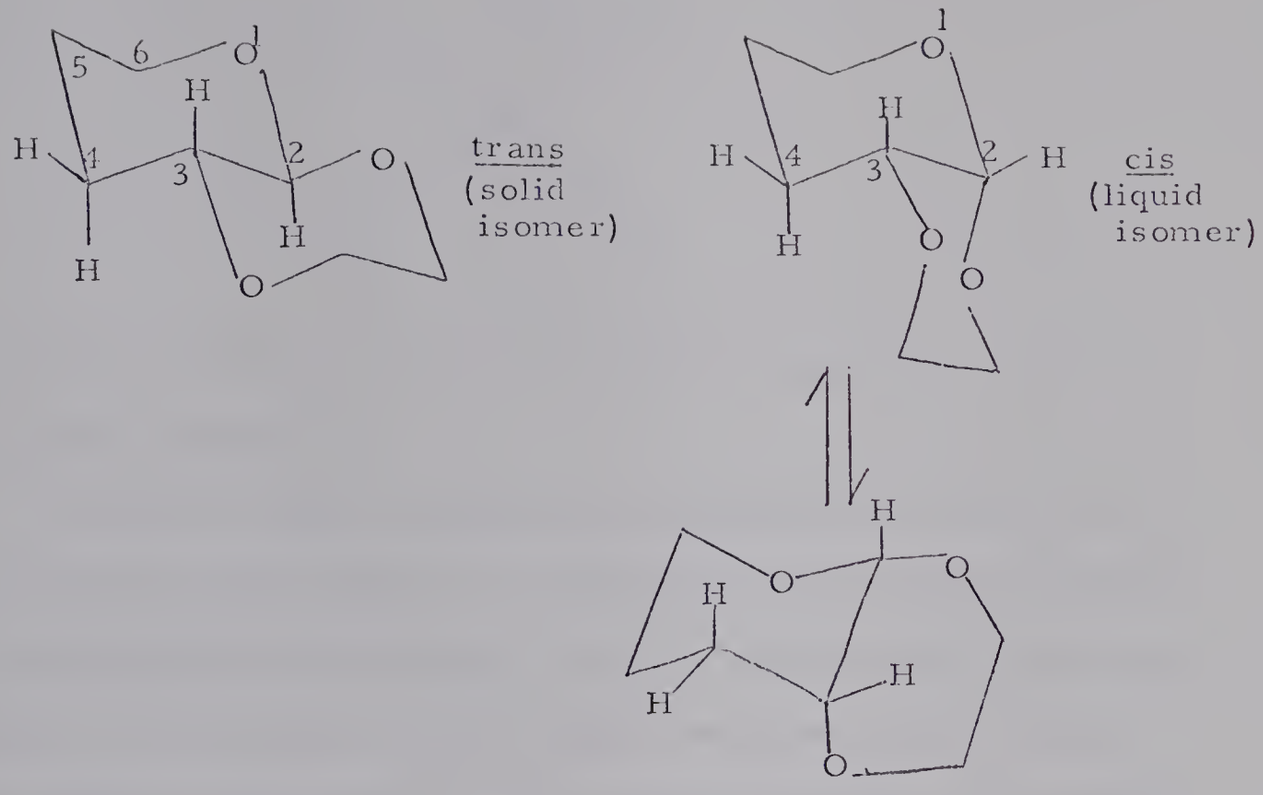
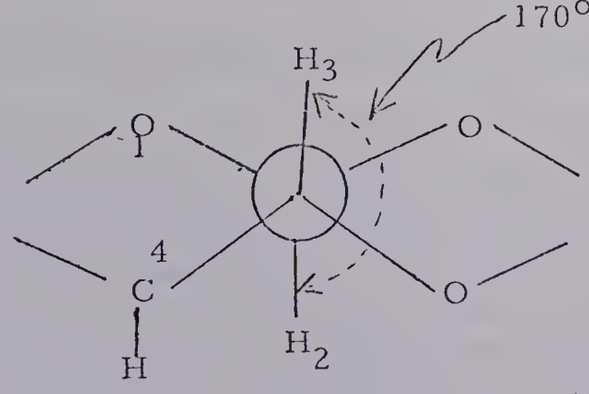
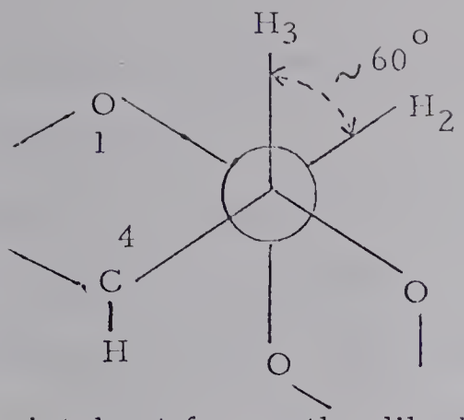


CHART 17

The trans isomer no doubt exists primarily in the preferred chair-chair form (Chart 17), in which, from examination of models, the dihedral angle between H-2 and H-3 lies between 170° and 180°. The models show that, even in the twist-boat form of the trans isomer,



the H-2, H-3 dihedral angle is still the same (170°-180°). In the preferred chair-chair conformations of the cis isomer (Chart 17), the H-2, H-3 dihedral angle is approximately 60°. With one ring in the twist-boat form, this angle is still the same (~ 60°). If both



rings are in the twist-boat form, the dihedral angle between H-2 and H-3 is very nearly 60°.*

In order for cis- and trans-tetrahydropyrano[2,3-b]-1,4-dioxane to be useful models for studying the conformational equilibria of 2,3-dialkoxytetrahydropyrans by n.m.r. spectroscopy, the experimentally observed spacing in the signal due to the anomeric proton must represent the actual H-2, H-3 coupling constant. It is possible that second-order effects (49) (i.e. "virtual coupling") arising from the C-4 protons could perturb the H-2 signal in which case the observed spacings might not be equal to $J_{2,3}$.

In order to determine whether some form of coupling (long-range or "virtual" coupling) exists between the C-2 and the C-4 protons in trans-tetrahydropyrano[2,3-b]-1,4-dioxane, the

* It is significant to bear in mind that in cis and trans decalin (of which these structures are analogs) in the chair-chair forms the trans-diaxial dihedral angle for H-9 to H-10 is 180°, while for the cis-isomer the axial-equatorial H-9, H-10 dihedral angle is 60°. However in the above oxygen heterocycles the ring oxygen atoms are expected to cause some bond-angle distortion. Therefore, it is unlikely that in rigid trans isomer (Chart 17) the trans-diaxial dihedral angle is exactly 180°. Similarly, the H-2, H-3 dihedral angle in the case of the cis isomer is expected to vary slightly from 60°.

following spin-decoupling experiments were carried out on a Varian HA-100 MHz spectrometer.

Irradiation of the C-2 proton at τ 5.84 caused a collapse in the multiplet 106 Hz upfield centered at τ 6.90, to a quartet with spacings of 10.5 Hz and 4.5 Hz. This quartet is undoubtedly due to the C-3 proton (see Fig. 2) and from foregoing considerations $J_{3,4a}$ = 10.5 Hz and $J_{3,4e}$ = 4.5 Hz. Irradiating the signal at τ 6.90 resulted in collapse of the H-2 doublet at τ 5.84 to a singlet and an observable simplification in the complex pattern in the vicinity of τ 8.0 which must be due to the C-4 protons. Irradiation at τ 8.0 resulted in collapse of the multiplet at τ 6.90 to a doublet of spacing 7.1 Hz ($J_{2,3}$), however there were no observable changes in the characteristics (i.e. spacing or signal shape) of the doublet due to H-2 at τ 5.84. Therefore the value 7.1 Hz is taken as the first-order coupling constant for $J_{2,3}$ in the trans compound.

Decoupling experiments were also attempted with the cis compound. These were unfortunately unsuccessful because the H-3 signal was obscured by signals due to the O-CH_2- protons. It is felt, however, that since the chemical shifts of C-2, C-3 and C-4 protons in cis-tetrahydropyrano[2,3-b]-1,4-dioxane are similar in the relative positions of their chemical shifts to those of the trans isomer any effect of virtual coupling of H-4 on the cis H-2,H-3 coupling should similarly be negligible.

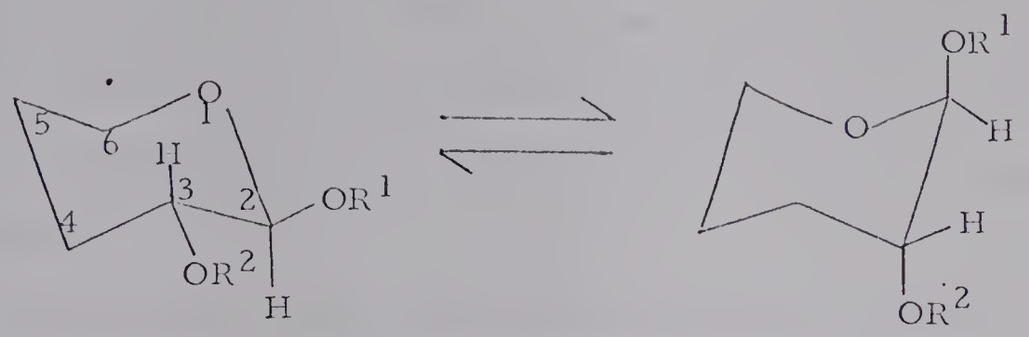
It is interesting to compare the trans-diaxial couplings of $J_{2,3}$ and $J_{3,4a}$ of 7.1 Hz and 10.5 Hz respectively. The geometric relationship between H-2 and H-3, and H-3 and H-4a should be quite

similar, hence the observed difference between $J_{2,3}$ and $J_{3,4a}$ of 3.4 Hz (10.5-7.1) must be due to the effect on these couplings of variations in the electronic environment surrounding the protons. The H-3 to H-4a and H-4e couplings are influenced by one oxygen atom on carbon 3 while the H-2 to H-3 coupling is reduced by 3.4 Hz due to the effects of three oxygen atoms.

In a similar manner $J_{3,4e}$ = 4.5 Hz in the trans compound can be compared with $J_{2,3}$ = 1.3 Hz in the cis compound since similar geometries are encountered. It is either an interesting coincidence or due to a significant interrelationship, that here too the variation in the number of oxygen atoms affecting the couplings results in a difference between coupling constants of 3.3 Hz. However, it is felt that observation of two similar cases does not warrant a quantitative generalization at present.

2. Estimation of conformational equilibria of trans-2,3-disubstituted tetrahydropyrans from the spin-spin couplings of their anomeric protons.

The trans-2,3-disubstituted tetrahydropyrans can be written in the alternate chair forms as shown in Chart 18 (it is assumed that the boat conformation need not be considered since it is energetically unfavorable). The n.m.r. spectrum for each of these compounds shows a distinct doublet for the anomeric C-2 proton (Table III). Spacings of the H-2 doublets, taken as $J_{2,3}$, fall within the range 3.0 Hz to 7.0 Hz. The observed value for $J_{2,3}$ depends upon the groups R^1 and R^2 present in the structures shown in Chart 18.



XX XXI

$R^1 = CH_3, H$

$R^2 = CH_3, C_2H_5, \underline{i}\text{-}C_3H_7, \underline{t}\text{-}C_4H_9, \beta\text{-}ClC_2H_4\text{-}$

CHART 18

The range of values for $J_{2,3}$ from the trans-2,3-disubstituted tetrahydropyrans compare to the H-2, H-3 coupling of 7.1 Hz obtained from trans-tetrahydropyrano [2,3-b]-1,4-dioxane (Chart 17), indicates that the former compounds are conformationally mobile. The observed spacings in the H-2 signals are undoubtedly the time-averaged values for the H-2, H-3 couplings derived from each of the conformers represented as XX and XXI in Chart 18.

Recently Bhacca and Horton (50), reported that the anomeric proton of β-D-ribopyranose tetra acetate showed a doublet with $J_{1,2}$* = 4.5 Hz in its 220 Hz nuclear magnetic resonance spectrum taken in acetone-d_6 solution at room temperature. However at -84° two doublets appeared for H-1* from the frozen conformers with $J_{1,2}$ =

* $J_{1,2}$ and H-1 in carbohydrate nomenclature correspond to $J_{2,3}$ and H-2 in the pyrans.

8.0 Hz and $J_{1',2'} \sim 1$ Hz. These authors concluded the value for $J_{1,2}$ (4.5 Hz) observed in the room temperature spectrum of the sugar represented a time-averaged value between the two conformational forms.

In the present work, attempts to "freeze out" the two conformers of trans-3-hydroxy-2-methoxytetrahydropyran were unsuccessful. At -60° the signal due to H-2 appeared unchanged compared to the room temperature signal. This is not surprising since in the highly substituted and presumeably less mobile "tetrahydropyran", β-D-ribopyranose tetraacetate, the signals due to the anomeric proton of each conformer coalesce at -60°(50). Since the actual values for $J_{2,3}$ from each conformer XX and XXI (Chart 18) were not available, the figures obtained from the model compounds were used to estimate the conformational equilibria of trans 2,3-disubstituted tetrahydropyrans.

The relative population for each of these conformers, was calculated using the following formula (51).

$$J_{obs} = J_{aa} X_{aa} + (1 - X_{aa}) J_{ee}$$

where X_{aa} = Mole fraction of the conformer with H-2 and H-3 trans-diaxial;

$X_{ee} = 1 - X_{aa}$ = Mole fraction of the conformer with H-2 and H-3 trans-diequatorial;

J_{aa} = Coupling constant corresponding to the conformer with H-2 and H-3 trans-diaxial;

J_{ee} = Coupling constant corresponding to the conformer with H-2 and H-3 trans-diequatorial;

J_{obs} = Coupling constant observed experimentally.

The values used for J_{aa} and J_{ee} were 7.1 Hz and 1.3 Hz. The values for J_{obs} were taken for each compound from the 60 MHz spectra*, where the spacings due to $J_{2,3}$ were read from the expanded (100 Hz sweep width) C-2 proton signals, so that they could be measured more accurately. In this way the values obtained are within the experimental limits of $\pm$ 0.1 Hz.

The values for X_{aa} were calculated from the formula on page 39 simplified to the form,

$$X_{aa} = \frac{J_{obs} - 1.3}{5.8}$$

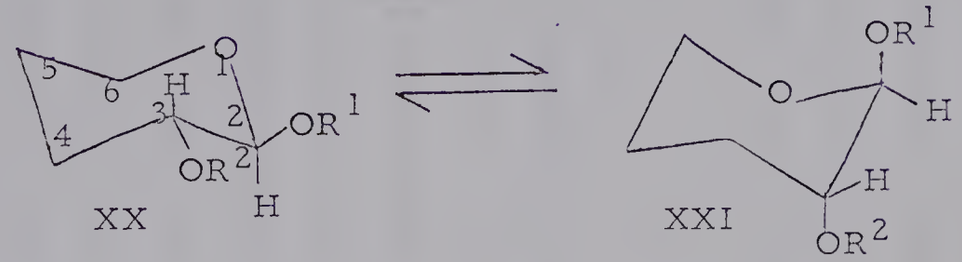
substituting 7.1 Hz and 1.3 Hz for J_{aa} and J_{ee}, respectively. These are given as mole per cent (X_{aa} x 100) in Table III.

Most likely the conformational equilibria values presented in Table III are most reliable for the series R^1 = alkyl, R^2 = CH_3 since in these molecules the chemical environment about C-2 and C-3 resembles most closely that in the model compounds. Also within each group (i.e. R^1 = alkyl, R^2 = H and R^1 = alkyl, R^2 = CH_3) comparing conformation equilibrium data between compounds is

* Several of the spectra were determined also at 100 MHz. These gave the same values for $J_{2,3}$ as those obtained from the 60 MHz runs.

TABLE III

N.M.R. Data and Calculated Conformational Equilibria for trans-2,3-Disubstituted Tetrahydropyrans.



Substituent, R^1	Substituent, R^2	Chemical Shift,[a] C-2 H	Coupling Constant,[c] J_{obs}, Hz	Calculated Relative Conformational Population,[d] % XX	% XXI
CH_3	H	5.79 (d)[b]	5.3	69	31
C_2H_5	H	5.72 (d)	5.5	72	28
i-C_3H_7	H	5.66 (d)	5.5	72	28
t-C_4H_9	H	5.61 (d)	7.0	98	2
ClC_2H_4	H	5.71 (d)	5.0	64	36
CH_3	CH_3	5.62 (d)	3.6	40	60
C_2H_5	CH_3	5.58 (d)	3.5	39	61
i-C_3H_7	CH_3	5.34 (d)	4.0	47	53
t-C_4H_9	CH_3	5.41 (d)	4.5	55	45

[a] The values presented above are derived from the 60 MHz n.m.r. spectra of the compounds in $CDCl_3$ referred to tetramethylsilane. All spectra were obtained at 34° (probe temperature).

[b] d = doublet. [c] Coupling constants were taken from the spacings due to the C-2 proton doublet, run on a 100 Hz sweep width. [d] % XX = X_{aa} x 100 and % XXI = $(1-X_{aa})$ x 100.

probably valid since deviations in chemical environment from the model compounds is reasonably the same for each member within a series.

Quantitatively, the most meaningful value calculated for the equilibrium ratio of the two conformers XX and XXI (Table III and Chart 18) is that for trans-2,3-dimethoxytetrahydropyran, since this molecule most resembles the model compound. Taking as the room temperature (actually probe temperature of ca. 34°) conformational equilibrium ratio 40:60 (Table III), the corresponding free-energy difference* between the two conformers is estimated to be $\Delta F^{o}_{25} = 0.24$ Kcal/mole. It is interesting that the favored conformation for trans-2,3-dimethoxytetrahydropyran is calculated to be the one in which the methoxy groups are in a diaxial arrangement. This is, however, to be expected since this compound is an analog of the pentopyranosides in which an anomeric alkoxy group is more stable in the axial, than in the equatorial, position. This unusual stereochemical situation is considered to be due to the "anomeric effect" (59), which will be discussed in detail in Chapter II.

A trend is observed in the data for the equilibrium between conformers XX and XXI, in Table III. In progressing from the methoxy group to the t-butoxy group at carbon 2, the proportion of conformer in which the C-2 and C-3 substituents are trans-diequatorial increases. This tendancy is apparently independent of the nature of the C-3 substituent. This can reasonably be explained on the basis of an increasing steric requirement for the C-2 substituent,

* From a table of ΔF^{o}-values calculated from percentages of more stable isomer at 25° (52).

in progressing from OCH_3 to $\underline{t}$-C_4H_9. Judging from the data in Table III a $\underline{t}$-butoxy group at the 2-position has a substantially greater steric requirement (98% equatorial) than a methoxy group (69% equatorial) at the same position. This stereochemical information will be useful for discussions in Chapter III and Chapter IV.

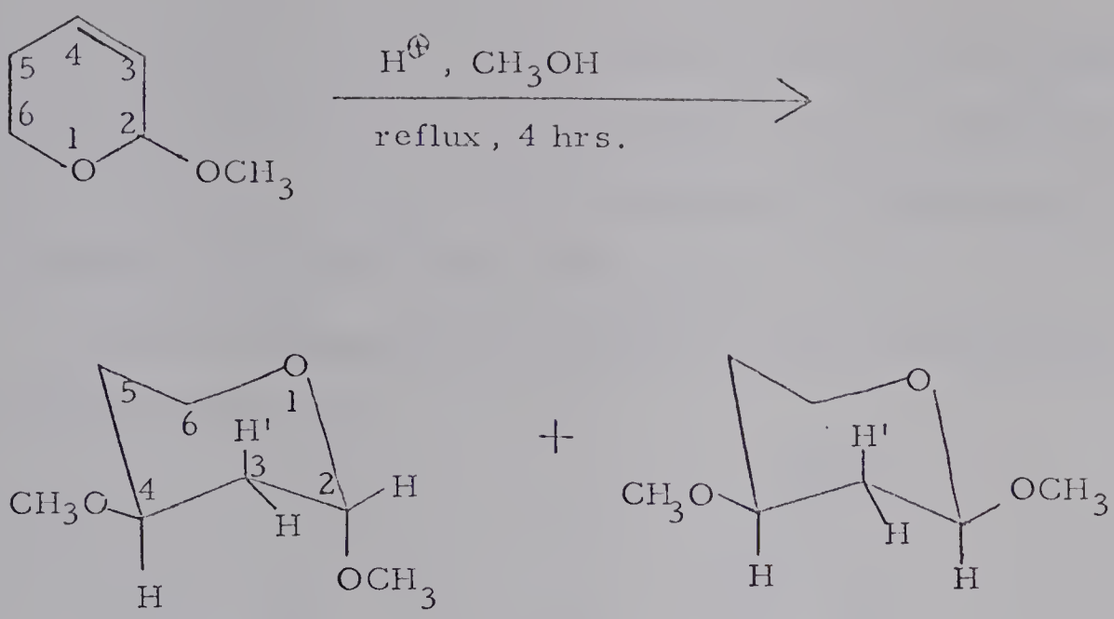
II. INTRODUCTION OF OXYGEN AT THE 2- AND 4-POSITIONS ON THE TETRAHYDROPYRAN RING.

The work described in Chapter I, shows that introduction of oxygen at positions 2 and 3 on the tetrahydropyran ring can now be more simply accomplished than was formerly possible.

A search of the literature failed to uncover any synthesis leading to simple tetrahydropyrans with oxygen at the 2- and 4-positions. The following discussion describes work in this laboratory which lead to the introduction of oxygen at the 2- and 4-positions on the tetrahydropyran ring.

A. Preparation of cis- and trans-2,4-dimethoxytetrahydropyran and cis- and trans-4-hydroxy-2-methoxytetrahydropyran.

When 2-methoxy-5,6-dihydro-2H-pyran (see Experimental) was heated in methanol in the presence of a catalytic amount of p-toluenesulfonic acid there was obtained by fractional distillation a 92% yield of a mixture of what proved to be trans- and cis-2,4-dimethoxytetrahydropyran in the ratio 4:1 respectively as shown in Chart 19. G.l.c. analysis of the crude material and pure distilled mixture showed these to be the only significant products of the reaction. Their separation was readily achieved by preparative g.l.c. on a column of 20% butanediol succinate on Gas-Chrom P.



trans-isomer	:	cis- isomer
4.0	:	1.0

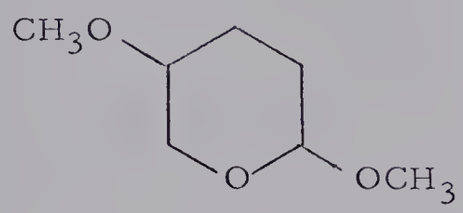
CHART 19

The mixture, as well as the separated components, were analyzed by n.m.r. spectroscopy (Figs. 4, 5, 6) and showed for the anomeric (C-2) proton signals for the major and minor constituents respectively, a triplet at τ5.28 ($J_{2,3'} = J_{2,3} = 2.9$ Hz) (Fig. 5) and a quartet at τ5.68 ($J_{2,3'} = 8.3$ Hz, $J_{2,3} = 2.8$ Hz) (Fig. 6). The spectra also indicated the presence of two methoxy groups on the basis of the integrated proton count. This, together with the elemental analysis, supports the structural assignment of a dimethoxytetrahydropyran for the product.

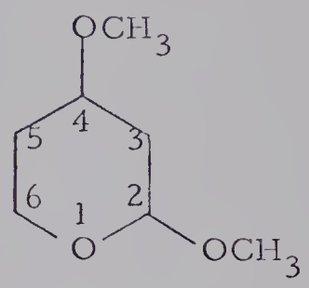
The n.m.r. spectrum of trans-2,3-dimethoxytetrahydropyran (Chapter I) shows a distinct doublet for the C-2 proton centered at τ5.62 ($J_{2,3} = 3.6$ Hz) (Table III, page 41) while a doublet due to H-2 in the cis isomer absorbs at τ5.41 ($J_{2,3} = 2.5$ Hz). The compound obtained by treating 2-methoxy-5,6-dihydro-2H-pyran

with acidic methanol (Chart 19) has distinctly different H-2 signals, indicating the presence of two C-3 hydrogens by virtue of the H-2 splitting patterns. Therefore, 2,3-dimethoxytetrahydropyran is not produced in the above (Chart 19) reaction.

Two remaining possible structures for the dimethoxytetrahydropyran obtained are,



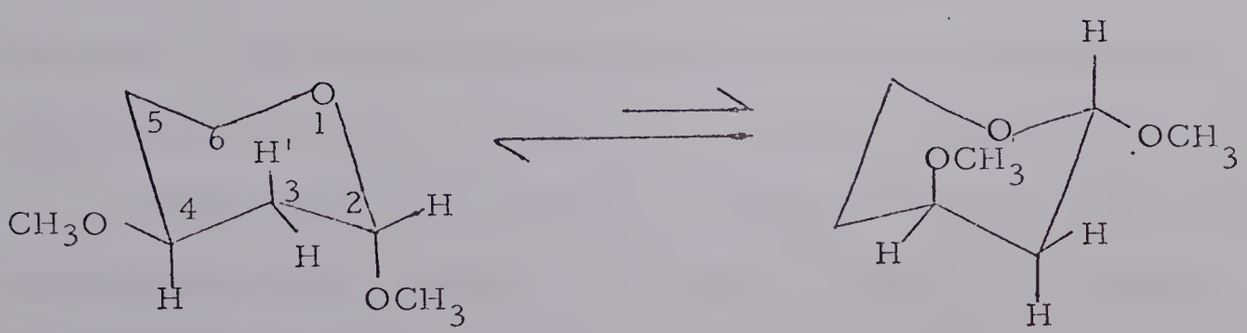
and



XXII XXIII

However, it is unlikely that 2,5-dimethoxytetrahydropyran XXII can be produced by this reaction (Chart 19). The structure of the product obtained is believed reasonably assigned as 2,4-diemethoxytetrahydropyran XXIII. This structural assignment will be discussed later from a mechanistic point of view.

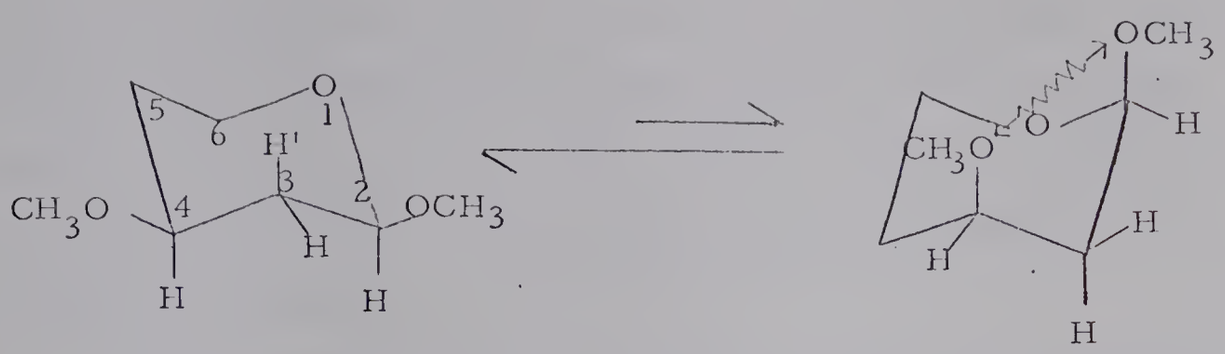
The structure for cis- and trans-2,4-dimethoxytetrahydropyran can be written in alternate chair conformations, as represented in Chart 20.



trans-isomer τ 5.28

$J_{2,3'} = J_{2,3} = 2.9$ Hz

(preferred)



cis-isomer τ 5.68

$J_{2,3'}$ = 8.3 Hz

$J_{2,3}$ = 2.8 Hz

(preferred)

CHART 20

The cis-isomer (Chart 20) undoubtedly exists primarily in the conformation in which both methoxy groups are in equatorial positions. In this conformation a highly unfavorable 1,3-diaxial interaction between the two methoxy groups is avoided (53). This conformation is consistent with the nuclear magnetic resonance spectrum (Fig. 6) in which the H-2 signal is a quartet centered at τ5.68 ($J_{2,3'}$ = 8.3 Hz; $J_{2,3}$ = 2.8 Hz). These values conform to the large trans diaxial H-2, H-3' coupling and the small H-2, H-3 axial-equatorial coupling expected by analogy with couplings found between H-2 and H-3 in the model compounds, cis and trans tetrahydropyrano [2,3-b]-1,4-dioxane (see Chapter I, pages 33 to 37).

The remaining H-2 signal, a triplet at τ 5.28, must be due to the trans isomer (Fig. 5). As shown in Chart 20, the trans-isomer can exist in what appears to be two equivalent conformations. However, the splitting pattern expected for H-2 wherein the C-2 OCH_3 group is equatorial, would be a quartet consisting of a large

and a small coupling, similar to that observed for the cis-isomer. The fact that a triplet for H-2 is observed (Fig. 5) for the trans-isomer, with $J_{2,3'} = J_{2,3} = 2.9$ Hz, indicates that in the preferred conformation the C-4 OCH_3 group is equatorial while the C-2 OCH_3 group is axial.

Each of the two separated isomers was allowed to isomerize at room temperature in methanol containing a small amount of p-toluenesulfonic acid. Equilibrium was reached within 7 days at room temperature (25°) and the equilibrium mixture in each case was found by n.m.r. and g.l.c. analysis to be composed of the trans and cis isomers in the ratio of 4:1 respectively.

The formation of only two components, trans- and cis-2,4-dimethoxytetrahydropyran, shows that a highly selective reaction had occurred between methanol and 2-methoxy-5,6-dihydro-2H-pyran. These results suggest that the double bond is selectively protonated. Apparently the more stable protonated state is that in which the carbon of the double bond more remote from the anomeric center becomes positive. This effect must be quite powerful since neither g.l.c. analysis nor n.m.r. spectroscopy indicated the presence of any 2,3-dimethoxy isomers (Chapter I) whose retention times and n.m.r. spectra are clearly different from those of the 2,4-dimethoxy compounds. Accordingly, one possible route leading to cis- and trans-2,4-dimethoxytetrahydropyran can be represented as shown in Chart 21.

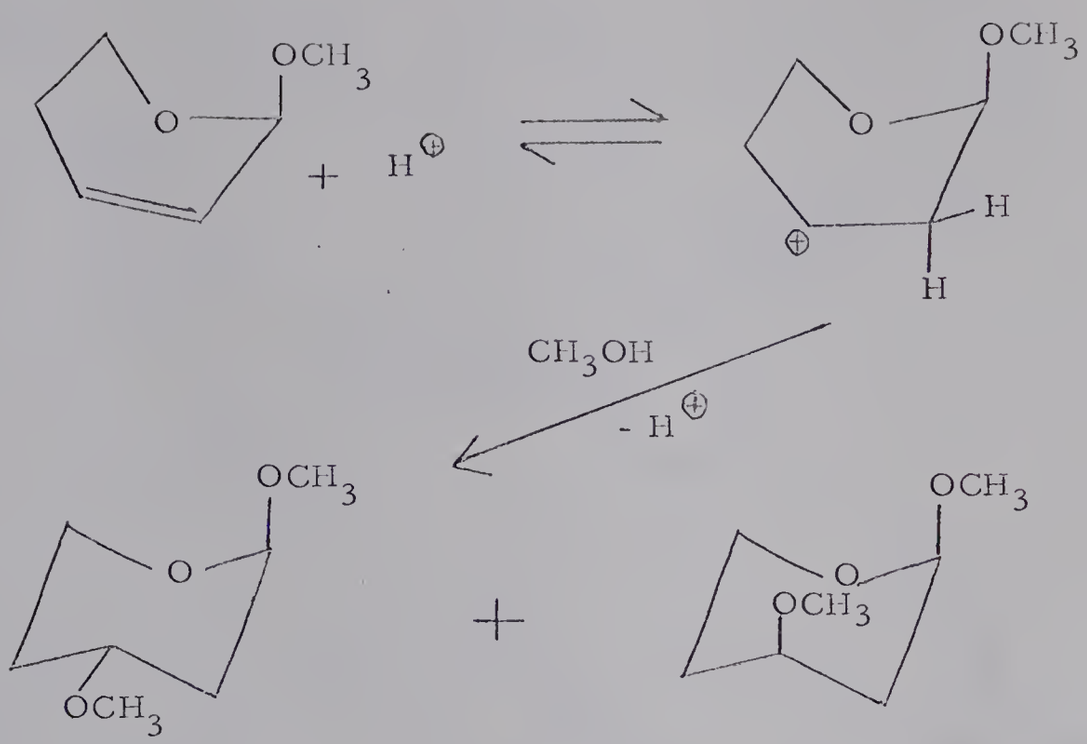
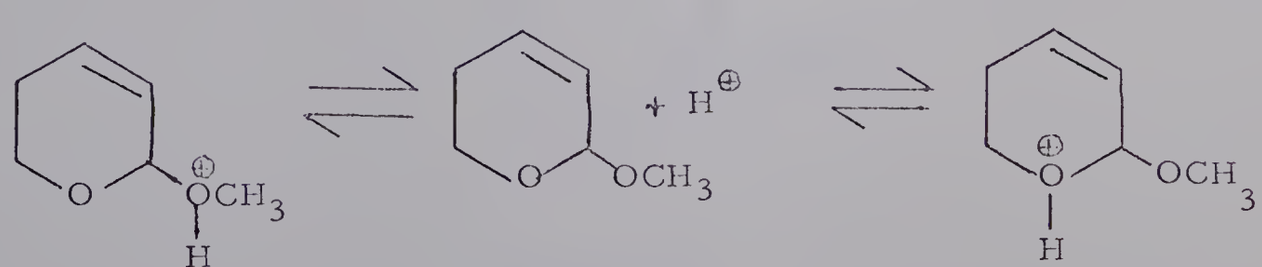


CHART 21

The reaction was carried out in an acidic medium in which acetals are known to be unstable. Accordingly, a second route to the formation of the 2,4-dimethoxytetrahydropyrans can be devised involving the acetal function. This is shown in Chart 22. The sequence is initiated by preferred protonation of the oxygen atoms rather than the double bond.



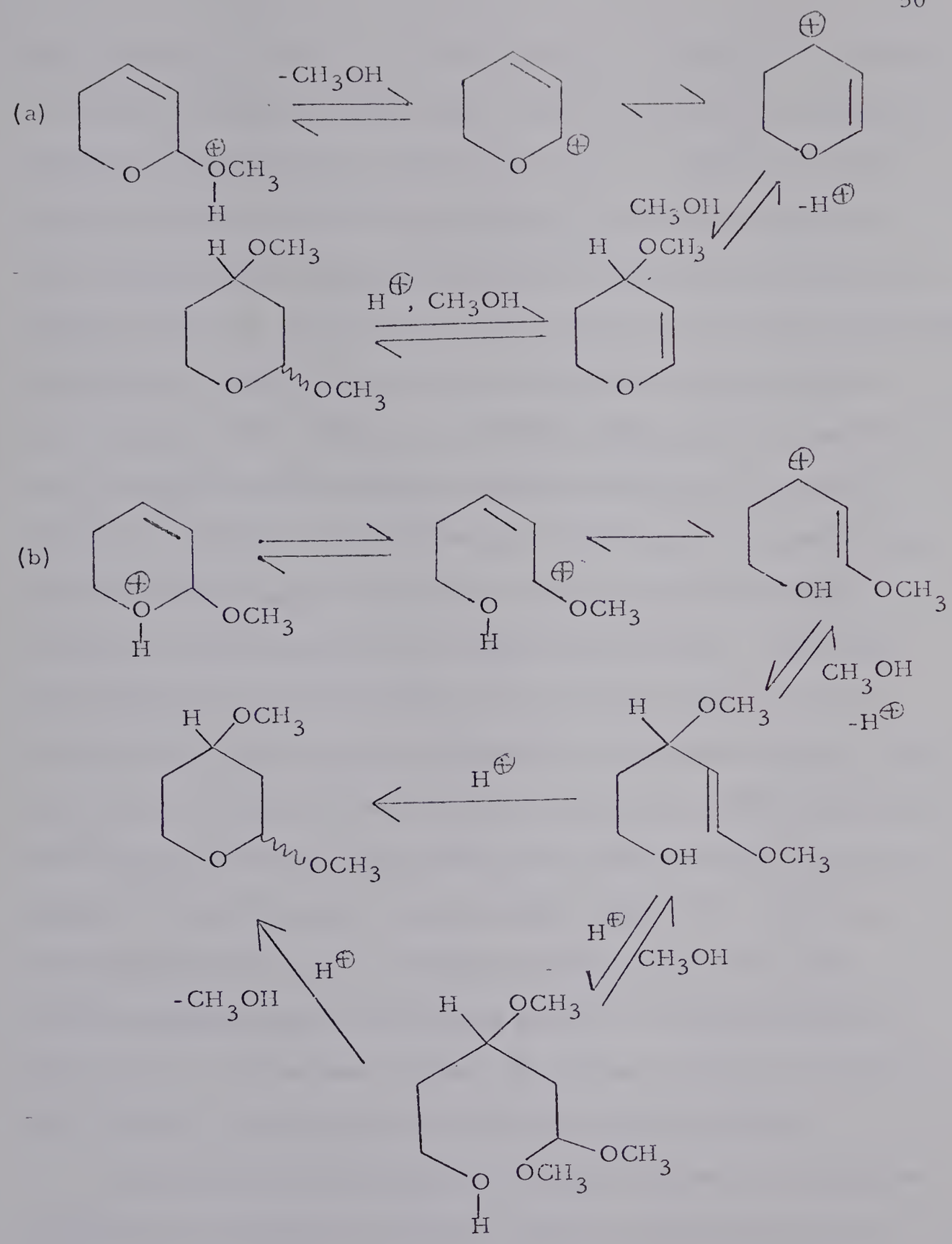
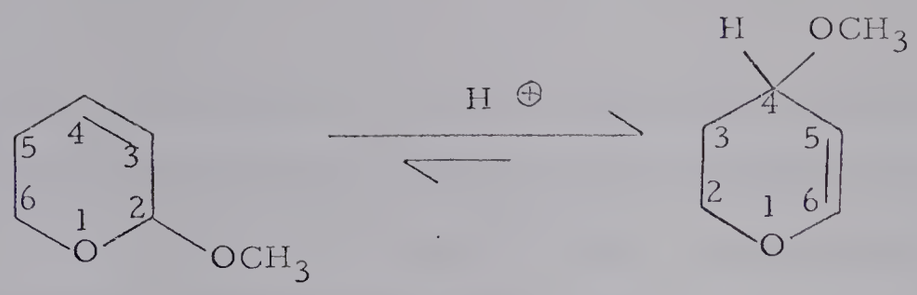

(a)
-CH3OH
OCH3
H
H OCH3
OCH3
CH3OH
-H⊕
H⊕, CH3OH
(b)
OH
OCH3
CH3OH
-H⊕
H⊕
-CH3OH

CHART 22

Two pathways, a and/or b in Chart 22 might be followed. In pathway a, removal of methyl alcohol would result in an allylic carbonium ion stabilized by participation of the oxygen atom. Attack by methyl alcohol at C-4 would result in 4-methoxy-2,3-dihydro-4H-pyran which might be thermodynamically more stable than 2-methoxy-5,6-dihydro-2H-pyran, since in the former molecule the unshared electrons of the hetero-oxygen atom could be associated with the orbitals of the π-bond. The 4-methoxy-2,3-dihydro-4H-pyran then would react as expected with methanol, under the influence of an acid catalyst, to produce 2,4-dimethoxytetrahydropyran. In pathway b, the ring is cleaved first, to yield an allylic carbonium ion which, as in a, is stabilized further by oxygen participation. Here also that product should accumulate in which reaction with methanol occurs at the carbon 4 giving a dimethoxy unsaturated alcohol. This would then readily cyclize to yield the 2,4-dimethoxytetrahydropyran. Possibly the dimethoxy olefin might react with methanol to form the acetal 3,5,5-trimethoxy-1-pentanol ((b), Chart 22). But it is expected that these acidic conditions would promote loss of the methoxy group and give the cyclized product, 2,4-dimethoxytetrahydropyran. The tendancy of such δ-hydroxy acetals to cyclize to a more stable tetrahydropyranyl ether has been shown (54).

An unsuccessful attempt was made to determine the relative stability of 2-methoxy-5,6-dihydro-2H-pyran and 4-methoxy-2,3-dihydro-4H-pyran by heating 2-methoxy-5,6-dihydro-2H-pyran in refluxing ether containing a catalytic amount of boron trifluoride ethereate. If indeed, the 4-methoxy-2,3-dihydro-4H-pyran is the



more thermodynamically stable isomer, as suggested above, in the absence of species that can act as nucleophiles (e.g. alcoholic solvent) it should accumulate at the expense of 2-methoxy-5,6-dihydro-2H-pyran. Only unchanged starting material and a quantity of a polymeric substance which analyzed for $C_6H_{10}O_2$ was obtained. Molecular weight analysis of this material suggested it to be a dimer. The formation of polymeric material is expected in view of the known reactivity of the analogous 3,4-dihydro-2H-pyran in the presence of acids (55).

Since methanolysis of 2-methoxy-5,6-dihydro-2H-pyran produced cis- and trans-2,4-dimethoxytetrahydropyran in good yield, it was thought possible to prepare 4-hydroxy-2-methoxytetrahydropyran, in a sequence of hydrolysis of the olefin followed by treatment of the intermediate compound with acidic methanol. An early report (56) states that attempts to convert 2-methoxy-5,6-dihydro-2H-pyran by mild acid hydrolysis to 5-hydroxy-2-pentenal resulted only in a polymeric product, unless hydrolysis was carried out in the presence of 2,4-dinitrophenylhydrazine. However, steam distillation of the hydrolysis mixture gave a 55% yield of 2,4-pentadienal, a product arising from dehydration of 5-hydroxy-2-pentenal (56).

In view of the knowledge gained from acid catalyzed

methanolysis of 2-methoxy-5,6-dihydro-2H-pyran, namely that a 2,4-dimethoxytetrahydropyran was formed, it is expected that by analogy the first step to the formation of the 2,4-pentadienal would be the formation of dihydroxytetrahydropyran.

This dihydroxytetrahydropyran should then undergo dehydration to 2,4-pentadienal as shown in Chart 23, routes a and d. (page 54).

Attempts in this laboratory to hydrolyze 2-methoxy-5,6-dihydro-2H-pyran in 0.1 N sulfuric acid at 95°-100° gave as the only isolable product 2,4-pentadienal (isolated as the 2,4-dinitrophenylhydrazone) along with some polymeric material. Such vigorous conditions were then discarded in favor of room temperature hydrolysis of 2-methoxy-5,6-dihydro-2H-pyran in the presence of the acidic ion-exchange resin, Amberlite IR 120 ($H^{\oplus}$). After removal of the ion-exchange resin by filtration, and distillation of water under vacuum, a viscous oily residue remained. Treatment of this residue with acidic methanol gave a mixture shown by gas-liquid chromatography to consist of 5 components. Three of the components could be identified by retention times as starting material, and trans- and cis-2,4-dimethoxytetrahydropyran. The remaining two substances, both of retention times greater than those of the other three constituents, were isolated by preparative g.l.c. as a mixture (2% overall yield) of cis- and trans-4-hydroxy-2-methoxytetrahydropyran. These were shown to be different from an isomeric mixture of authentic cis- and trans-3-hydroxy-2-methoxytetrahydropyran (Chapter I) by g.l.c. and n.m.r. analysis.

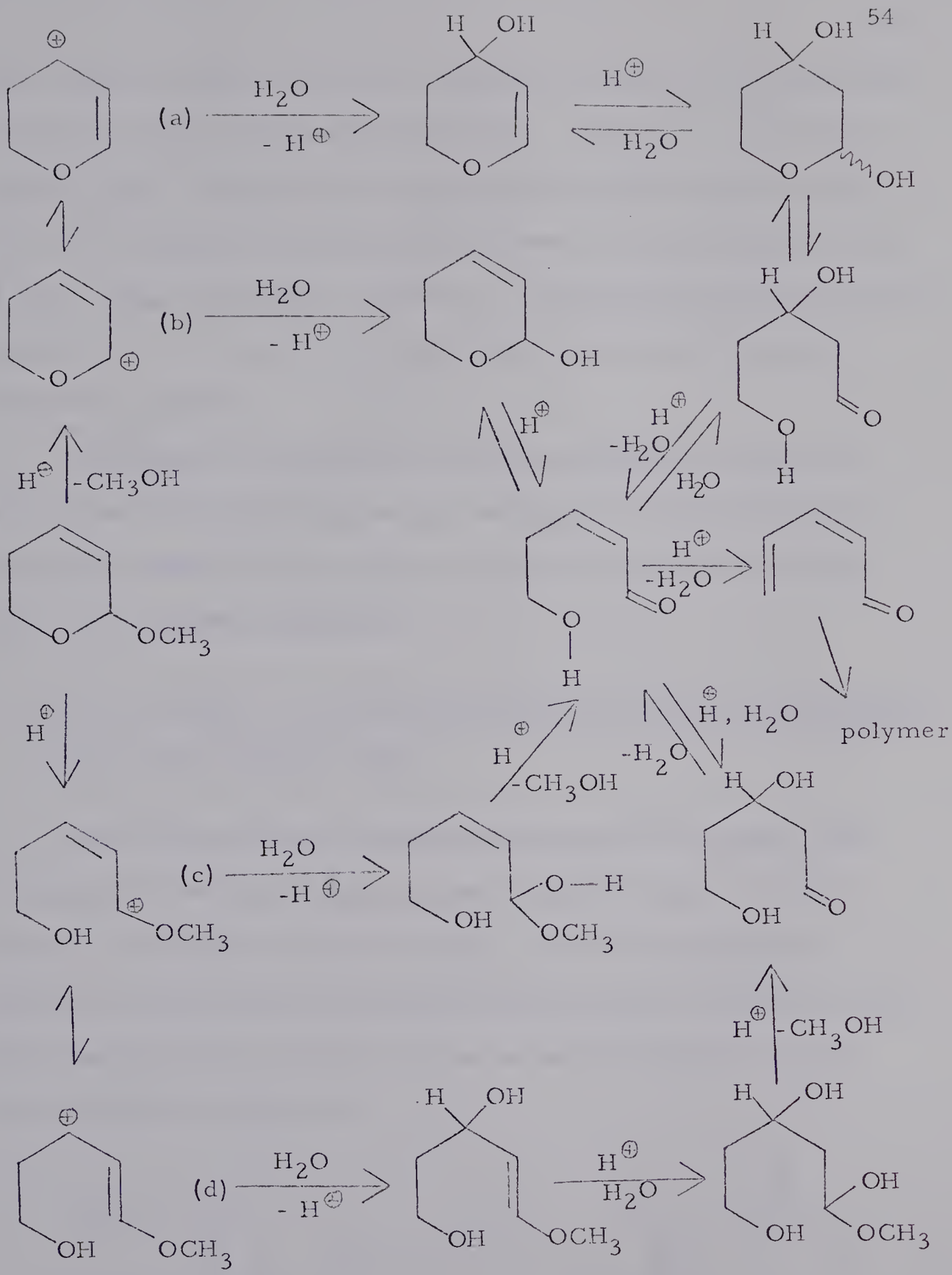

(a)
H_2O
$-H^{\oplus}$
$H^{\oplus}$
H_2O
(b)
H_2O
$-H^{\oplus}$
$H^{\oplus}$
$-CH_3OH$
$H^{\oplus}$
$-H_2O$
H_2O
$H^{\oplus}$
$-H_2O$
polymer
$H^{\oplus}$
$-CH_3OH$
$H^{\oplus}$, H_2O
$-H_2O$
(c)
H_2O
$-H^{\oplus}$
(d)
H_2O
$-H^{\oplus}$
$H^{\oplus}$
H_2O
$H^{\oplus}$
$-CH_3OH$

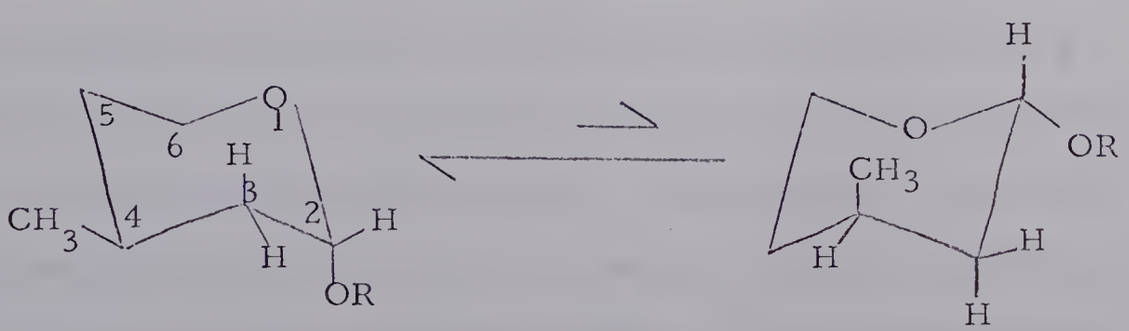
CHART 23

Both isomers of the 3-hydroxy compound had shorter retention times than the isomeric 4-hydroxy compounds. The n.m.r. spectra of cis- and trans-4-hydroxy-2-methoxytetrahydropyrans showed two sets of overlapping multiplets in the anomeric proton region (τ5.10-τ5.35). Cis- and trans-3-hydroxy-2-methoxytetrahydropyrans show doublets at τ 5.44 and τ 5.75 respectively, for the H-2 protons (Table III, page 41).

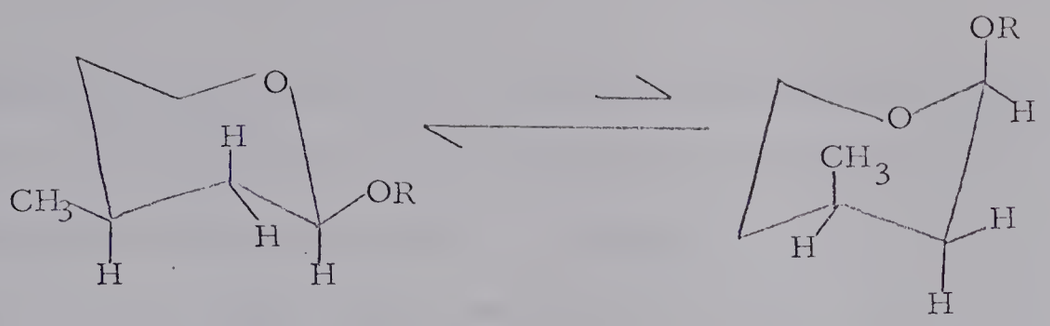
Methylation of the mixture of cis- and trans-4-hydroxy-2-methoxytetrahydropyrans gave cis- and trans-2,4-dimethoxytetrahydropyran whose n.m.r. and g.l.c. spectra were identical with those from authentic material.

B. Cis- and trans-2,4-dimethoxytetrahydropyrans as models for the study of the anomeric effect.

Recently Anderson and Sepp (57) proposed 2-acetoxy- and 2-methoxy-4-methyltetrahydropyrans as useful models of carbohydrates, to study the anomeric effect. One of the important features of these molecules was the methyl group on carbon 4, which they reasonably felt should occupy an equatorial position in each isomer, shown in Chart 24.



trans-isomer



cis-isomer

R = CH_3, CH_3CO

CHART 24

The n.m.r. spectrum of the H-2 proton for each isomer seemed to support their view (57) that the C-4 CH_3 group biased the pyran ring in the favored conformations (Chart 24). Indeed these compounds proved useful in obtaining information that could be related to analogous carbohydrates. However, very few carbohydrates possess a C-3 methyl group (C-4 in pyrans) and so these compounds, are not suitable as models for most of the carbohydrates. An oxygen atom at the 4-position would more closely approximate the structure of carbohydrates in general. On this basis then it is thought that 2,4-dimethoxytetrahydropyran should be a more widely applicable carbohydrate model than is 2-methoxy-4-methyltetrahydropyran.

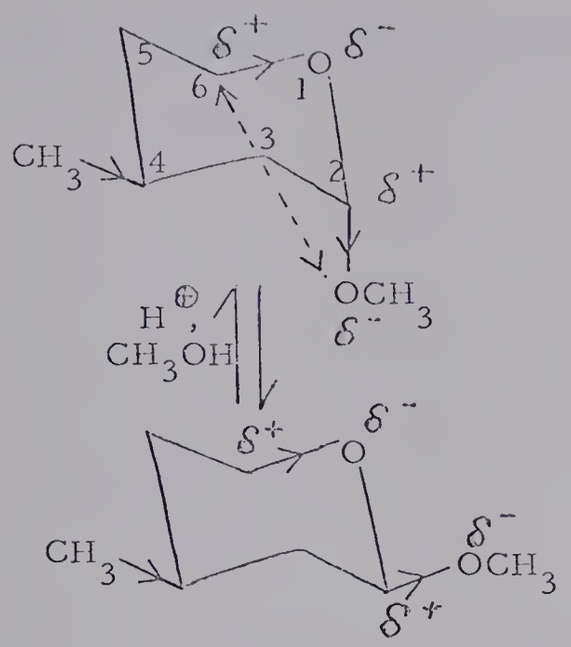
When either cis- or trans-2,4-dimethoxytetrahydropyran was dissolved in anhydrous methanol at 25° containing some p-toluenesulfonic acid, an equilibrium mixture of isomers was obtained in which the trans:cis ratio was 4:1. This shows that the axial C-2 methoxy group is favored over the equatorial C-2 methoxy to the extent of $-\Delta F^{\circ} = 0.82$ Kcal/mole*. The anomeric effect

* The value for ΔF° was obtained from tables. See reference (52).

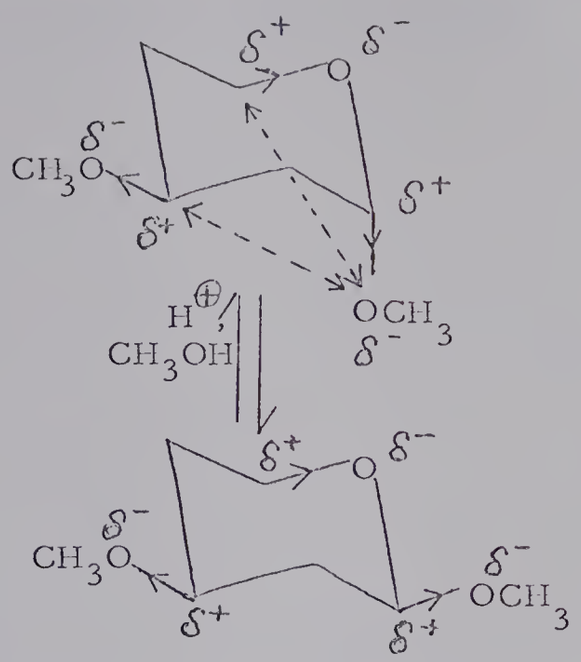
quantitatively is equal to the sum of the experimentally determined free-energy difference ($-\Delta F^{o}$) between the anomers and the A-value of the C-2 methoxy group (57). Using an A-value of 0.6 Kcal/mole (58) for the methoxy group, Anderson and Sepp (57) have calculated the anomeric effect in 2-methoxy-4-methyltetrahydropyran (in methanol) to be 1.08 Kcal/mole. In the present work, using the same value of 0.6 Kcal/mole for the A-value of the methoxy group (cf. 0.7 Kcal/mole, ref. 53, page 44), the anomeric effect in 2,4-dimethoxytetrahydropyran is calculated to be (0.6 + 0.82) = 1.42 Kcal/mole. The difference between this value and that of Anderson and Sepp is most likely due to the nature of the C-4 substituent. The fact that replacement of the C-4 methyl group by the methoxy substituent <u>increases</u> the anomeric effect by $\sim$ 0.3 Kcal/mole tends to support Lemieux's view (59, 60) that the anomeric effect is caused by some form of intramolecular dipolar interaction. This has been stated (60) more specifically as follows:

> " . . . it is possible that there exists a fairly strong hydrogen bond between the aglycon and the 5-hydrogen (which corresponds to H-6 in pyran nomenclature) since almost surely a lone pair orbital of an axial oxygen atom at the 1-position (C-2 in pyrans) is directed toward the 5-hydrogen."

From structures in Chart 25 it is quite clear that the electron attracting methoxy group at C-4 creates a partial positive charge on this carbon atom, just as the ring oxygen causes a partial positive charge on C-6. The positive character of C-4 and C-6 provides



anomeric effect = 1.08 Kcal/mole



anomeric effect = 1.42 Kcal/mole

CHART 25

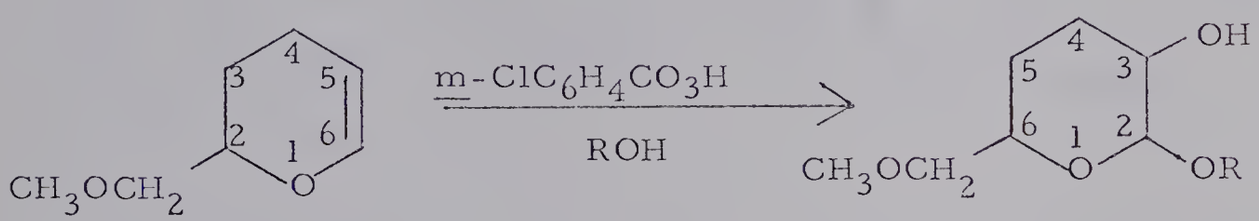
greater stabilization of the partially negatively charged C-2 oxygen substituent when it is in the axial rather than in the equatorial position (Chart 25).

On the other hand with a methyl group on C-4 little or no polarization (in contrast with the C-O bond case) is expected to exist at this carbon. Hence in this molecule only C-6 exhibits positive character and the C-2 methoxy group is consequently somewhat less stabilized in the axial orientation compared to the 2,4-dimethoxy-tetrahydropyran case. Therefore, the difference between the values for the anomeric effect obtained by Anderson and Sepp in 2-methoxy-4-methyltetrahydropyran (1.08 Kcal/mole), and in 2,4-dimethoxy-tetrahydropyran (1.42 Kcal/mole) (Chart 25) may represent the energy of stabilization contributed by an equatorial C-4 alkoxy group

(C-3 in carbohydrates) to an axial alkoxy group on the anomeric (C-2) carbon.

III. INTRODUCTION OF OXYGEN AT THE 2- AND 3-POSITIONS OF THE 6-METHOXYMETHYL-SUBSTITUTED TETRAHYDROPYRAN RING.

The facile and stereospecific synthesis of trans-2-alkoxy-3-hydroxytetrahydropyran (Chapter I, Section A) from 3,4-dihydro-2H-pyran prompted extension of this procedure to preparation of the 6-methoxymethyl analogs, as shown in Chart 26.



R = CH_3, t-C_4H_9

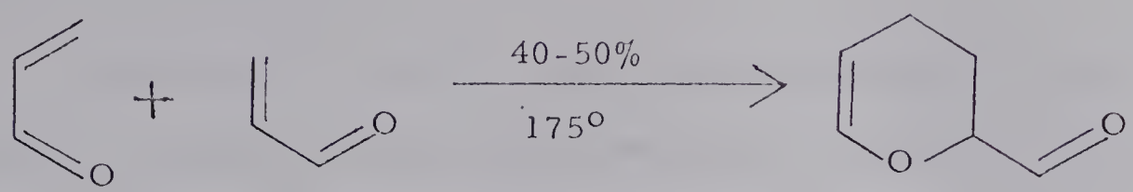
CHART 26

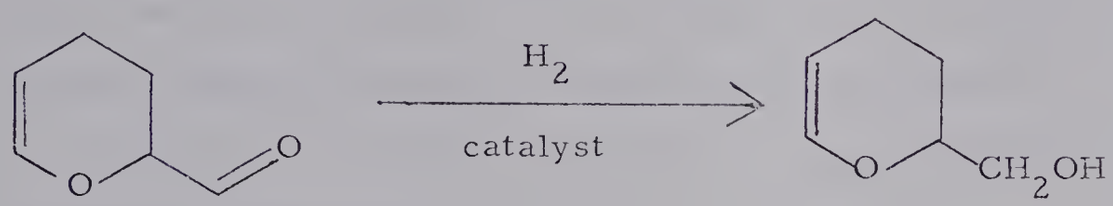
A. Preparation, structure and conformational preference of 2-alkoxy-3-hydroxy-6-methoxymethyltetrahydropyrans.

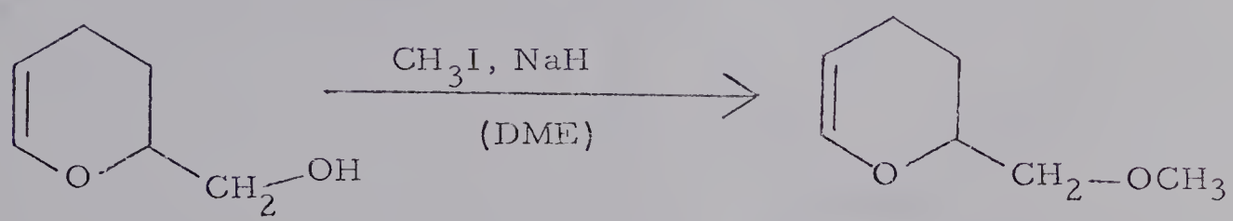
2-Methoxymethyl-3,4-dihydro-2H-pyran was prepared in 91% yield from the corresponding alcohol by methyl iodide-sodium hydride alkylation (61). The alcohol 2-hydroxymethyl-3,4-dihydro-2H-pyran was, until recently, commercially available*. However it is no longer being produced. The commercial preparation involved a Diels-Alder self-condensation of acrolein to the dimer (21)

* Shell Development Co., Emoryville, California.

which in turn could be reduced to the "dimer alcohol", 2-hydroxymethyl-3,4-dihydro-2H-pyran (Chart 27).







DME = Dimethoxyethane

CHART 27

Treatment of a methanolic solution of 2-methoxymethyl-3,4-dihydro-2H-pyran with m-chloroperoxybenzoic acid at -10° gave, after workup, a 73% yield of an isomeric mixture of two 3-hydroxy-2-methoxy-6-methoxymethyltetrahydropyrans. Analysis of the oil by g.l.c. using a column of 20% butanediol succinate on Gas-Chrom P at 195° showed two peaks with areas in the ratio of 82:18.

The n.m.r. spectrum of the product in $CDCl_3$ solution showed

signals for two anomeric protons, C-2 H, at τ 5.93 (doublet, $J_{2,3}$ = 7.2 Hz) and τ 5.37 (doublet, $J_{2',3'}$ = 3.0 Hz), in the ratio of 80:20 respectively (Table IV).

In Chapter I, section A, it was shown that under similar reaction conditions to those described above 3,4-dihydro-2H-pyran gave a product in which the hydroxyl and alkoxy groups were in a trans arrangement. Therefore, since there is no reason why a change of mechanism should occur it is expected that 2-methoxymethyl-3,4-dihydro-2H-pyran similarly would give the two isomers in which the 3-hydroxyl and 2-methoxy groups are in a trans relationship, as indicated in Chart 28.

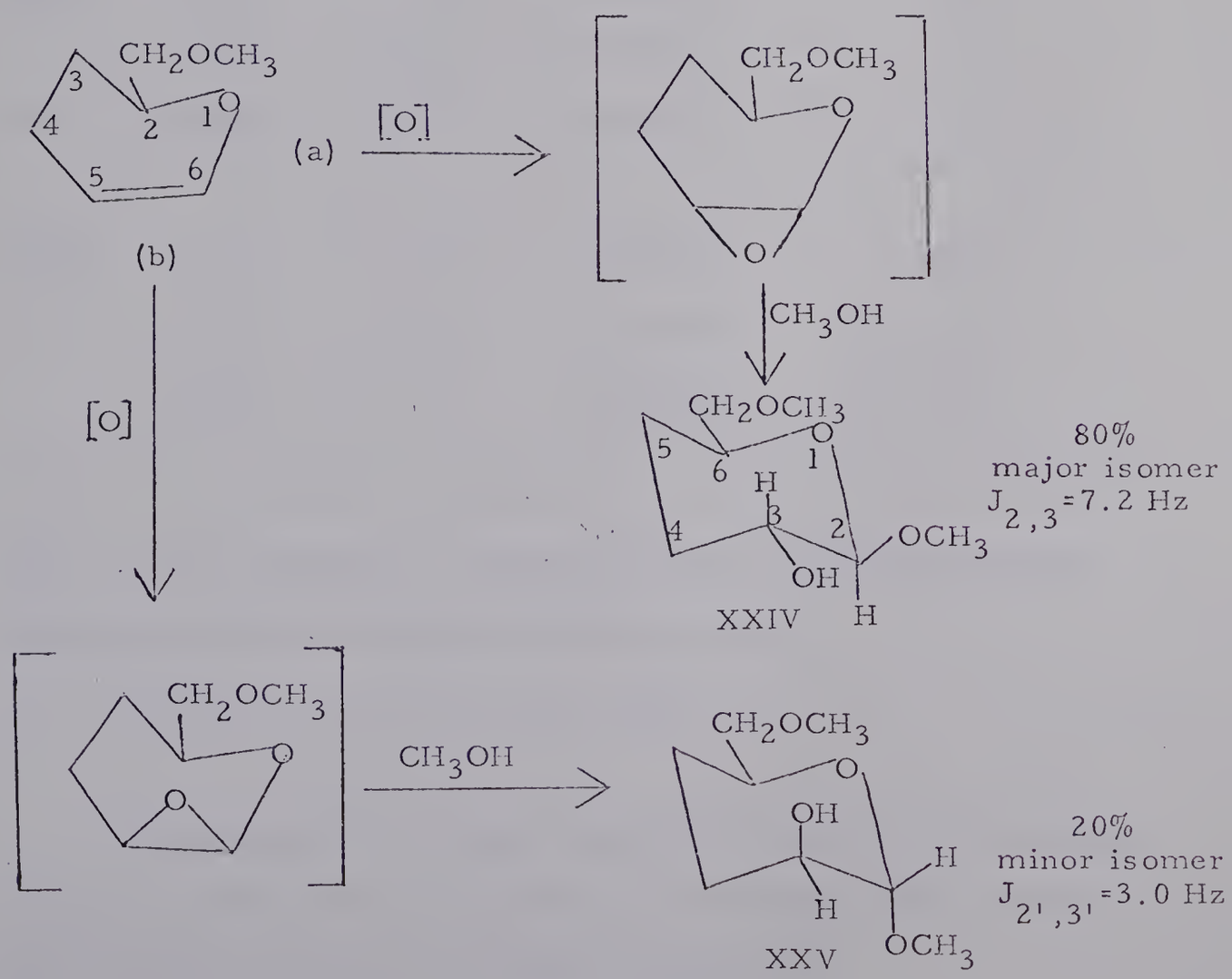
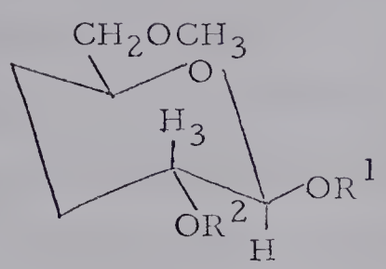


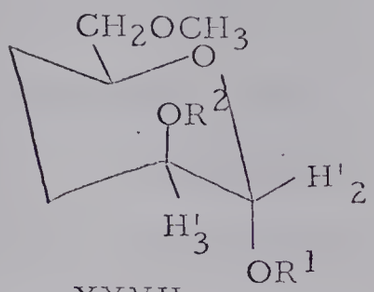
CHART 28

TABLE IV

N.M.R. Data for 2,3-Disubstituted 6-Methoxymethyltetrahydropyrans.



XXVI



XXVII

	Substituent		Chemical Shift[a]	Coupling Constant[b]
	R^1	R^2	τ C-2 H	$J_{2,3}$, Hz
XXVI	CH_3	H	5.93 (d)	7.2
	CH_3	CH_3	5.82 (d)	7.0
	t-C_4H_9	H	5.50 (d)	7.2
XXVII	CH_3	H	5.37 (d)	3.0
	CH_3	CH_3	5.35 (en)[c]	$\frac{w}{2}$ = 3.0
	t-C_4H_9	H	5.04 (en)	$\frac{w}{2}$ = 3.0

[a]Run in $CDCl_3$ solutions; tetramethylsilane as internal standard.

[b]Obtained from the expanded 60 MHz spectrum.

[c]en = envelope; $\frac{w}{2}$ = width at half height.

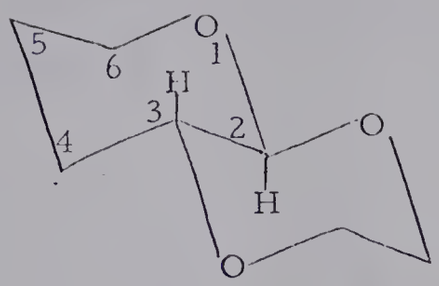
Due to the steric requirement of the 6-methoxymethyl group it may be safely assumed (62) that the two isomers XXIV and XXV (Chart 28) are in the conformations indicated (59).

Based on the signals due to the anomeric proton, the n.m.r. data supports the configurational assignments since in carbohydrates, of which these compounds are analogs, the validity of configurational assignments on a similar basis remains unchallenged today (35, 41). Clearly the high field C-2 H signal with $J_{2,3} = 7.2$ Hz indicates a trans-diaxial configuration for C-2 H and C-3 H, while the low field C-2 H signal with $J_{2',3'} = 3.0$ Hz is consistent with a diequatorial arrangement for these protons (see the discussion in Chapter I, Section B, part 1).

Methylation (61) of the isomeric mixture of 3-hydroxy-2-methoxy-6-methoxymethyltetrahydropyrans gave in 85% yield an 85:15 mixture of isomeric 2,3-dimethoxy-6-methoxymethyltetrahydropyrans. The n.m.r. spectrum of this compound shows a major and minor signal for the anomeric (C-2) protons at τ 5.82 (doublet, $J_{2,3} = 7.0$ Hz) and τ 5.35 (envelope, $\frac{W}{2} = 3.0$ Hz), respectively (Table IV).

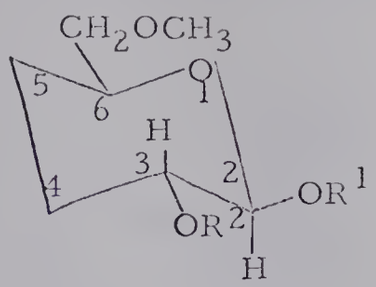
When the above reaction (Chart 26, R = t-C_4H_9) was carried out in the presence of t-butyl alcohol compounds analogous to XXIV and XXV, Chart 28 were obtained in the isomeric ratio of 80:20. The n.m.r. spectral data for this series of compounds is summarized in Table IV.

The almost constant values obtained for the H-2, H-3 couplings, in the above compounds is interesting (Table IV). The values for $J_{2,3}$ for compounds of the series with configurations as represented by XXVI in Chart 29, are in the range 7.0-7.2 Hz (Table IV).



XXVIII

$J_{2,3}$ = 7.1 Hz



XXVI

$J_{2,3}$ = 7.0-7.2 Hz

R^1 = CH_3, t-C_4H_9

R^2 = H, CH_3

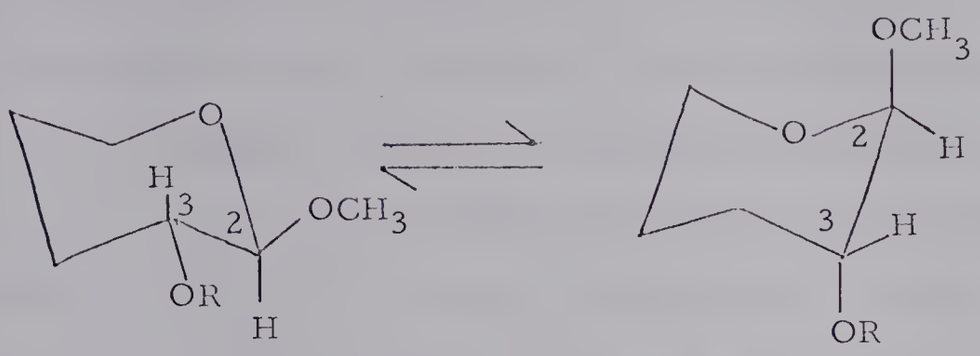
CHART 29

For trans-tetrahydropyrano [2,3-b] -1,4-dioxane (XXVIII, Chart 29) the value for $J_{2,3}$ is 7.1 Hz. It has already been pointed out that the rigid nature of this compound results in a H-2, H-3 dihedral angle of 170°-180° (Chapter I, Section B).

On the basis of structural consideration the 6-methoxymethyl compound XXVI (Chart 29) is not expected to have the same high restriction of rotation about the C-2, C-3 bond, as is found in its bicyclic analog, XXVIII. However, the chemical environments surrounding H-2 and H-3 in compounds XXVIII and XXVI are almost identical. Now if the coupling constant $J_{2,3}$ is taken as a measure of the H-2, H-3 dihedral angle then because of the similarity of the coupling constants ($J_{2,3}$ = 7.0-7.2 Hz), it must be concluded that the 6-methoxymethyl group in XXVI imposes a similar degree of conformational rigidity on the pyran ring as exists in compound XXVIII. Accordingly, the amount of "twist", if any, in compounds XXVI and XXVIII is also about the same.

For the conformationally mobile compounds trans-3-hydroxy-

-2-methoxytetrahydropyran and trans-2,3-dimethoxytetrahydropyran (Chapter I),



$R = H$, $J_{2,3} = 5.3$ Hz

$R = CH_3$, $J_{2,3} = 3.6$ Hz

the difference between the H-2, H-3 couplings (5.3-3.6) is 1.7 Hz (Table III). Since these H-2, H-3 couplings result from time-averaged values from the two conformations, the change in $J_{2,3}$ corresponding to the change OH $\longrightarrow$ OCH_3 at carbon 3 is probably due to attendant shifts in the conformational equilibrium, variations in "electronegativity" effects, or some combination of both.

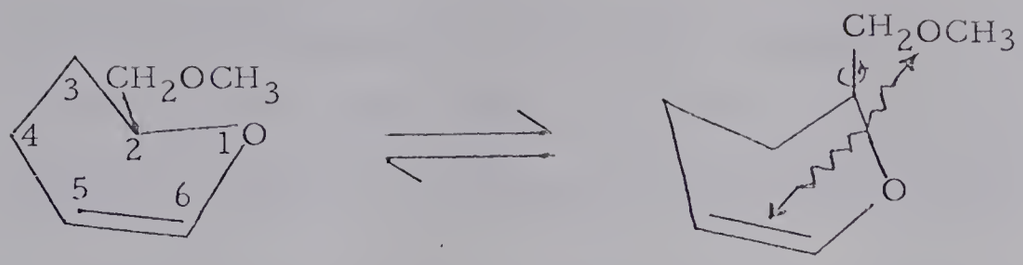
However, for compound XXVI (Chart 29) with $R' = CH_3$, when R^2 is changed from $R^2 = H$ to $R^2 = CH_3$ the difference between corresponding H-2, H-3 couplings (Table IV) is small (~ 0.2 Hz). These observations can be rationalized on the basis that the 6-methoxymethyl group in XXVI biases the pyran ring in the conformation in which the C-6 substituent is almost entirely equatorial, regardless of the nature of the group (OH $\longrightarrow$ OR) attached to carbon 2. Furthermore it appears that "electronegativity" effects are not responsible for the variation in H-2, H-3 coupling, due to changes in the C-3 substituent in the trans-2,3-disubstituted tetrahydropyrans.

For if such effects operated in these compounds similar substituent effects should be observed for their 6-methoxymethyl analogs.

A similar comparison between the H-2, H-3 couplings for the pair of compounds trans-2-t-butoxy-3-hydroxytetrahydropyran ($J_{2,3}$= 7.0 Hz) and trans-3-hydroxy-2-methoxytetrahydropyran ($J_{2,3}$= 5.3 Hz), and the corresponding pair of the 6-methoxymethyl analogs (XXVI, R^1=CH_3, R^2=H, $J_{2,3}$= 7.2 Hz and R^1= t-C_4H_9, R^2=H, $J_{2,3}$= 7.2 Hz) is revealing. This data tends to indicate that the 2-t-butoxy group in the 2,3-disubstituted tetrahydropyran biases the pyran ring to nearly the same extent as does the 6-methoxymethyl group in XXVI. Furthermore it appears that in XXVI for R^1= H and R^2=CH_3, the preferred conformation is as equally populated as for R^1=H and R^2= t-C_4H_9 (i.e. both compounds are conformationally fixed to the same extent).

B. Stereochemical control in the formation of the isomeric 2-alkoxy-3-hydroxy-6-methoxymethyltetrahydropyrans.

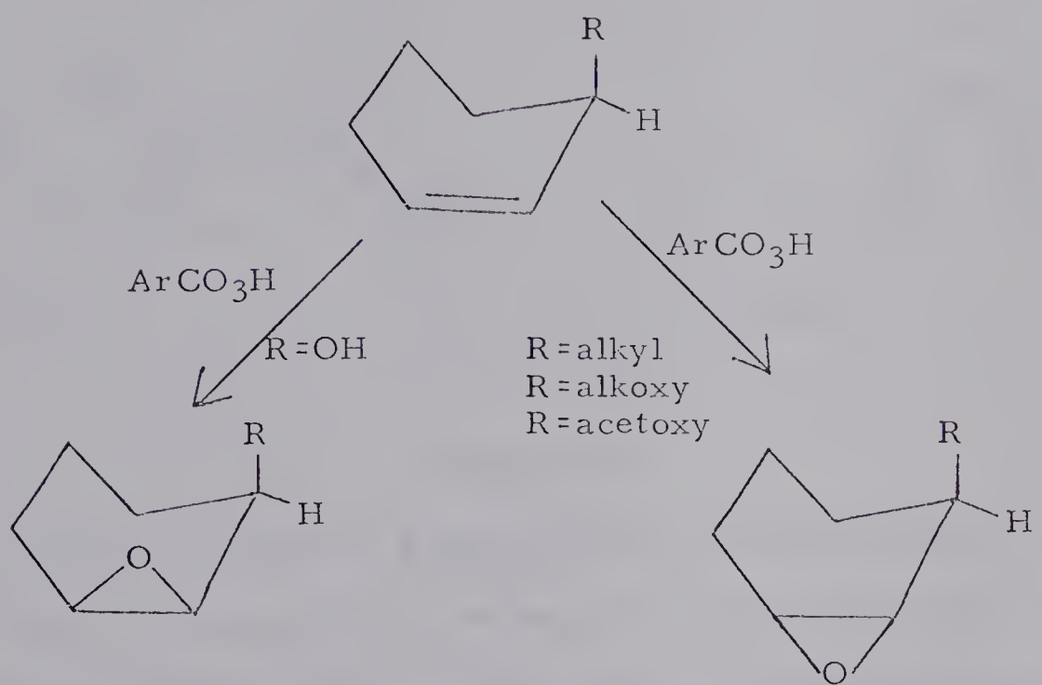
The proportion of each isomer obtained(XXIV and XXV in Chart 28) is interesting. It is well known (32, 46, 47) (and will be discussed at length in Chapter IV) that the ring substituents in cyclohexenes, exert a substantial steric influence during epoxidation of these compounds. On a similar basis it seems reasonable that the 2-methoxymethyl group, which should be able to attain a quasi-axial conformation in 2-methoxymethyl-3,4-dihydro-2H-pyran, should exert some steric influence.



Examination of models shows that this conformation is readily attainable. Also the quasi-axial 2-methoxymethyl group in rotation about the CH_3OCH_2—C-2 bond blocks access to the double bond from the side of the ring on which the C-2 substituent exists. Therefore, the fact that XXVI is predominantly formed when 6-methoxymethyl-3,4-dihydro-2H-pyran is treated with m-chloroperoxybenzoic acid can be explained as arising from stereochemical control exerted by the 2-methoxymethyl group, in directing epoxidation of the double bond primarily to the side of the ring opposite to the C-2 substituent.

IV. STEREOCHEMICAL AND ELECTRONIC EFFECTS IN THE PREPARATION AND $LiAlH_4$ REDUCTION OF CIS- AND TRANS-2-ALKOXY-3,4-EPOXYTETRAHYDROPYRANS.

It is known that in systems containing the cyclohexene ring, the C-3 substituent controls the direction of peroxy acid epoxidation of the double bond (Chart 30).



cis-epoxide

trans-epoxide

CHART 30

If the C-3 substituent is an hydroxyl group the peroxy acid is found to attack the double bond on the side cis to the hydroxyl substituent (32, 47). This is attributed to hydrogen bonding between the hydroxyl group and the incoming peroxy acid (47) (Chart 31).
If the C-3 substituent is alkoxy, acetoxy or alkyl, epoxidation occurs preferentially trans to the C-3 substituent (47) presumably because of steric hindrance to approach by the peroxy acid.

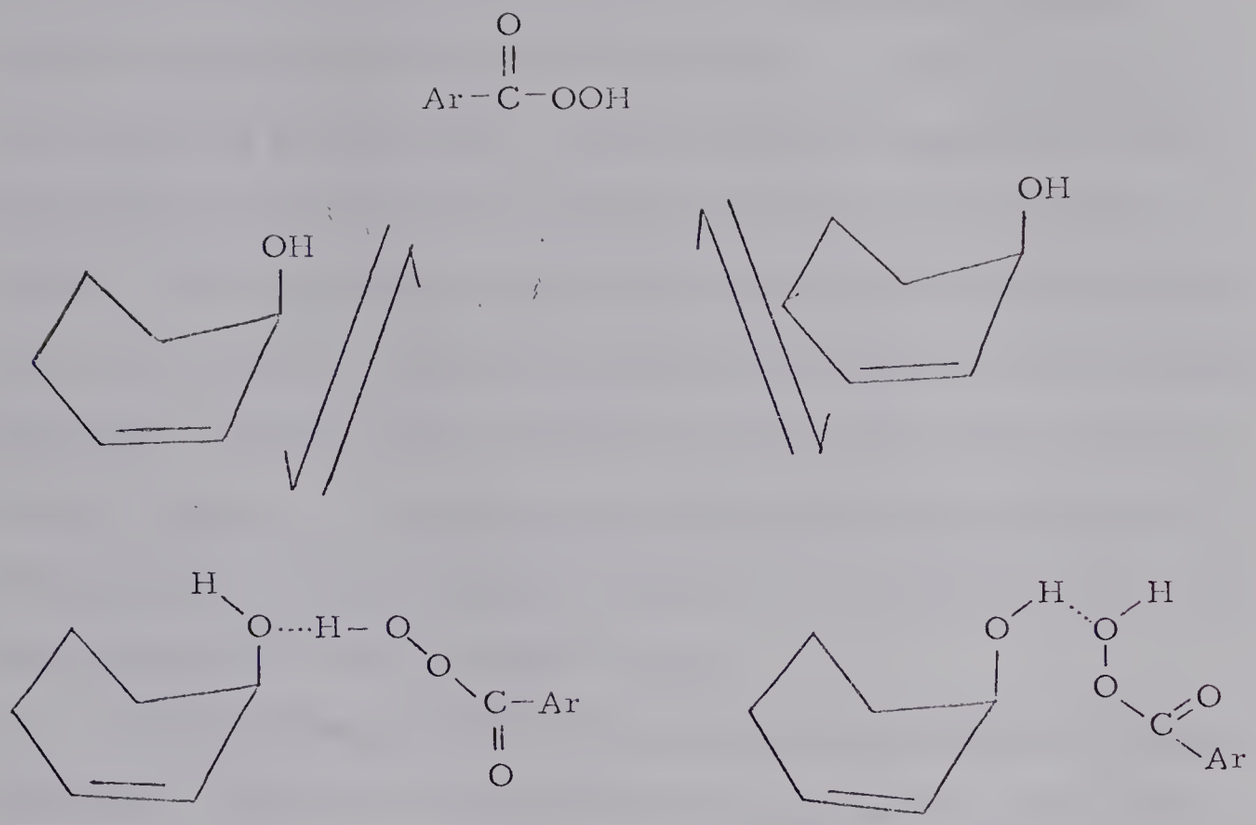
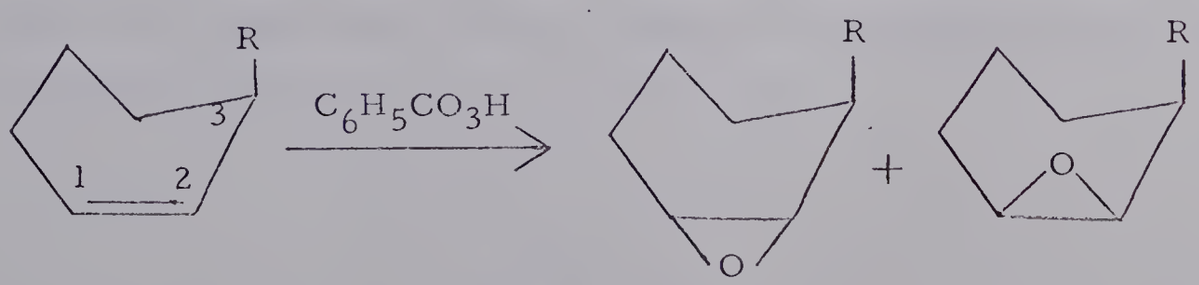


CHART 31

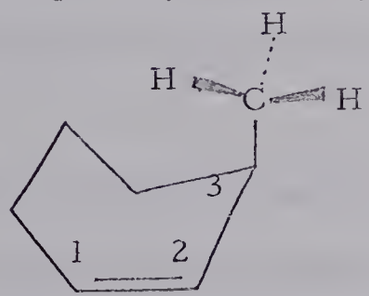
More recently (64) 3-substituted cyclohexene oxides, prepared by treatment of appropriate substituted cyclohexenes with peroxybenzoic acid were studied in detail. The trans to cis ratios of the isomeric mixture of epoxides were accurately determined by g.l.c.. The following results were obtained:



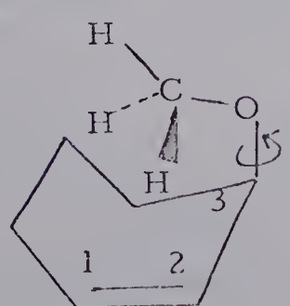
	trans-epoxide	cis-epoxide
R	%	%
CH_3	53	47
OCH_3	82	18

If it is assumed that in the above example the observed isomeric ratios result from steric hindrance by the C-3 substituent to formation of a cis epoxide, it must concluded that the C-3 $-CH_3$ exerts less stereochemical control in epoxidation than does the C-3 $-OCH_3$. This may seem surprising in view of the fact that a methyl group has a greater steric requirement in cyclohexane than a methoxy group (53). Yet the above epoxidation data suggests that an allylic methoxy group (i.e. a methoxy group situated in the position α to a double bond) exerts greater steric control over epoxidation than does a correspondingly situated methyl group.

Examination of models of 3-substituted cyclohexene oxides is revealing. The C-3 $-CH_3$ group in the quasi-axial position does not prevent access to the double bond from the same side of the cyclohexene ring occupied by the methyl group.



These models also show that the freely rotating OCH_3 group on C-3, when in the quasi-axial position, projects the methyl group over the double bond effectively blocking access to it.



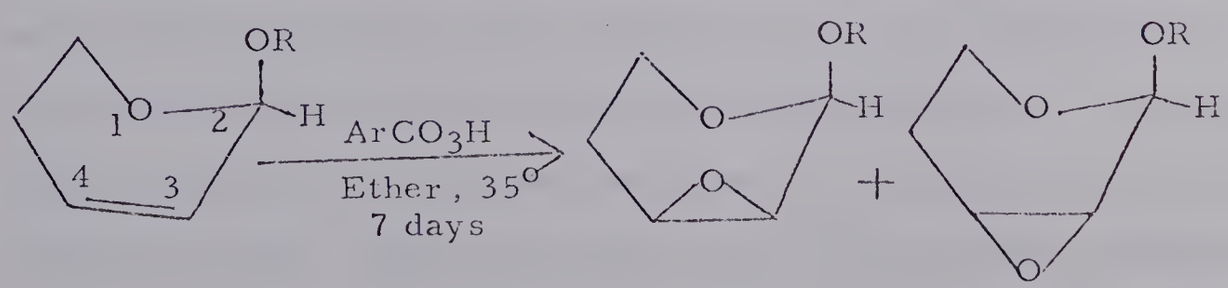
The above comparison appears to explain the observed results of epoxidation of 3-substituted cyclohexenes.

In order to discover whether similar stereochemical effects are present in pyran analogs of the 3-substituted cyclohexenes discussed above, epoxidation of 2-alkoxy-5,6-dihydro-2H-pyrans with m-chloroperoxybenzoic acid was carried out. The results of these experiments are described in the following section.

A. Stereochemical control in the preparation of cis- and trans-2-alkoxy-3,4-epoxytetrahydropyran.

2-Alkoxy-5,6-dihydro-2H-pyrans were epoxidized in this laboratory in the following manner. In ether solution, at ~35°, the reaction between m-chloroperoxybenzoic acid and either 2-methoxy- or 2-t-butoxy-5,6-dihydro-2H-pyran* produced in each case an 80-85% yield of a mixture of cis- and trans-2-alkoxy-3,4-epoxy-tetrahydropyrans.

The trans isomer predominated to the extent of 75% and 90% for the 2-methoxy and 2-t-butoxy compounds respectively (Chart 32).



$R=CH_3$	25%	75%
$R=C(CH_3)_3$	10%	90%

CHART 32

* For the preparation of 2-alkoxy-5,6-dihydro-2H-pyrans see the Experimental section.

The cis and trans isomers of the 2-methoxy compound could be readily separated by preparative gas-liquid chromatography and the physical characteristics determined. The trans- and cis-isomeric mixture of the 2-t-butoxy homologue however, on the two different columns, 25% carbowax 20M on Gas Chrom P, and 20% Butanediol succinate on Gas Chrom P, gave two slightly overlapping peaks which were in the ratio of 9:1 respectively. Gas-liquid chromatographic separation of the major component was accomplished, but isolation, by the same method, of the minor component in an isomerically pure state was quite difficult and therefore abandoned. The n.m.r. spectrum of the cis-trans isomeric mixture of the 2-methoxy and of the 2-t-butoxy epoxides obtained from the reaction agreed with the spectra of the separated compounds. The signals for the anomeric C-2 protons could be used to characterize the configurations of the cis and trans isomers once the configurations had been determined by chemical means. The n.m.r. spectra of these epoxides is of particular interest and will be discussed in detail, later.

The configurational assignments were obtained from the $LiAlH_4$ reduction of the epoxides. Reduction of the 3,4-epoxy-2-methoxytetrahydropyran isomer obtained in major proportion gave a nearly quantitative yield of a compound identical in every respect to trans-3-hydroxy-2-methoxytetrahydropyran, previously prepared by a different route. (The preparation and configurational arrangement of this compound as well as that for trans-2-t-butoxy-3-hydroxytetrahydropyran, has already been discussed in Chapter I of this work.) From the known reactions of epoxides with nucleophilic reagents (16)

it follows that this 3,4-epoxy-2-methoxytetrahydropyran must be the trans isomer. Both g.l.c. analysis and the n.m.r. spectrum of the product obtained from the hydride reduction showed no detectable amount of the cis isomer or any other product to be present.

Similarly, reduction of the major isomer of the cis-trans mixture of 2-t-butoxy-3,4-epoxytetrahydropyran gave exclusively, and in ~90% yield, the trans-2-t-butoxy-3-hydroxytetrhydropyran identical in all respects with an authentic specimen. Accordingly, the 3,4-epoxy precursor was trans-2-t-butoxy-3,4-epoxytetrahydropyran.

Hydride reduction of the 3,4-epoxy-2-methoxytetrahydropyran isomer obtained in minor amount from the epoxidation reaction mixture gave only the known cis-3-hydroxy-2-methoxytetrahydropyran. G.l.c. analysis of the reaction mixture showed no evidence for the presence of the trans isomer or any other product. It follows then that this 3,4-epoxy-2-methoxytetrahydropyran must have been the cis isomer.

Authentic samples of the other possible products of reduction, cis- and trans-4-hydroxy-2-methoxytetrahydropyran (Chapter II), were compared by g.l.c. and n.m.r. analysis with the compounds obtained from the epoxides above. All four isomers could be readily distinguished in a mixture. Within the experimental limits of analysis only one product could be detected from $LiAlH_4$ reduction of each of the isomeric epoxides.

Finally, reduction with $LiAlH_4$ of the 9:1 mixture of the two isomeric 2-t-butoxy-3,4-epoxytetrahydropyrans gave, according to

g.l.c. and n.m.r. analysis, a 9:1 mixture of trans- and cis-2-t-butoxy-3-hydroxytetrahydropyrans. The retention times and signals due to the anomeric protons were the same as those found for authentic trans-2-t-butoxy-3-hydroxytetrahydropyran and its contaminating (2-3%) cis isomer. Neither g.l.c. nor n.m.r. analysis showed evidence for the presence of any other compound which might indicate that hydride reduction of the 9:1 mixture of epoxides had produced as well some of the isomeric 2-t-butoxy-4-hydroxytetrahydropyrans.

In Chapters I and III n.m.r. studies of the conformational equilibrium of 2,3-disubstituted tetrahydropyrans lead to the conclusion that a C-2 t-butoxy group had a greater steric requirement (98% equatorial) than a C-2 methoxy group (69% equatorial) (Table III, page 41). This is consistent with the above findings that epoxidation of 2-alkoxy-5,6-dihydro-2H-pyrans are strongly subject to steric influences, since the presence of a t-butoxy group at carbon 2 produces a greater proportion of trans epoxy isomer than the C-2 methoxy group (Chart 32).

B. Stereochemical and electronic effects in the $LiAlH_4$ reduction of cis- and trans-2-alkoxy-3,4-epoxytetrahydropyran.

It is known that the reaction of anions with the epoxide ring produces predominantly that compound resulting from trans diaxial opening of the ring (47, 65, 66). The flexibility of the 2-alkoxy-3,4-epoxytetrahydropyran ring would permit trans diaxial epoxide ring opening in either of the two half-chair conformers XXIX and XXX,

Chart 33, and thus both trans-4-hydroxy-2-alkoxytetrahydropyran and trans-3-hydroxy-2-alkoxytetrahydropyran could be formed.

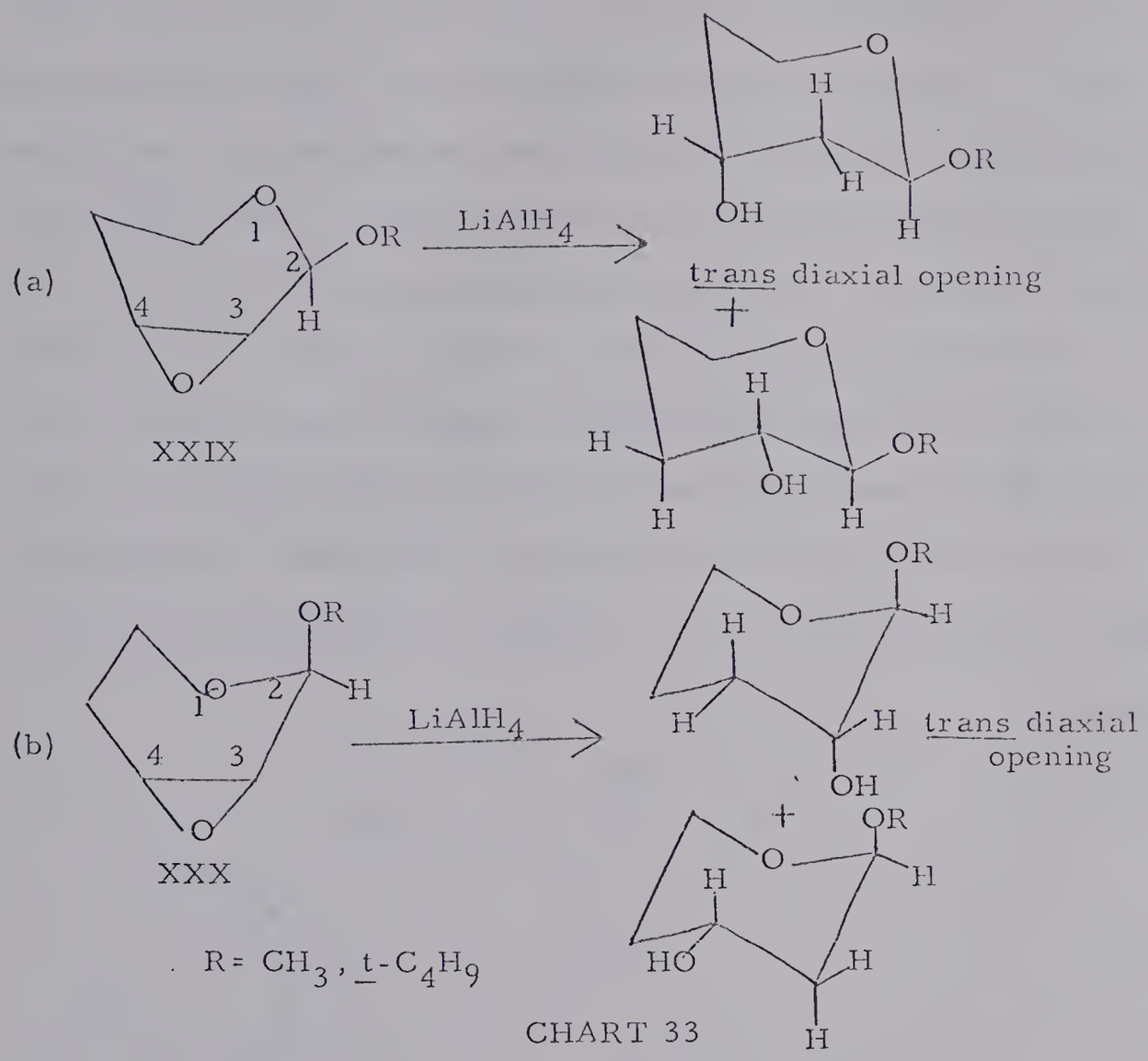
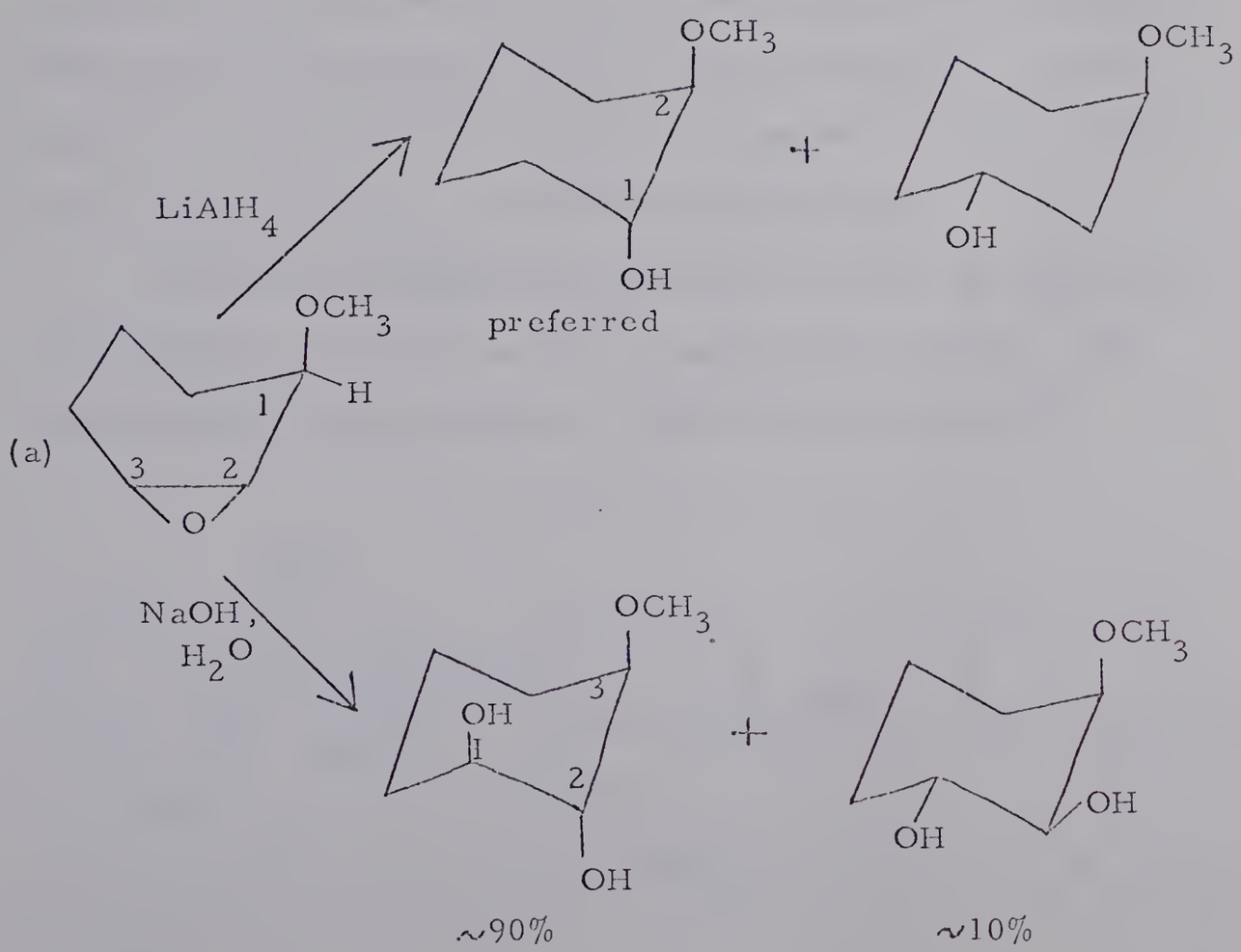


CHART 33

In the present work, however, it has been found that attack by $LiAlH_4$ appears to occur completely on the carbon atom of the epoxide ring remote from the C-2 alkoxy group (Chart 33, route (b)).

Such a directive influence could be due to either steric or electronic factors or a combination of both. The flexibility of the ring in trans-2-alkoxy-3,4-epoxytetrahydropyran may be somewhat limited due to the anomeric effect (59, 67, 68, and Chapter II, Section B) which would favor conformer XXX (Chart 33). In this

conformation, the steric hindrance caused by the quasi-axial 2-alkoxy group to the approach of $LiAlH_4$ to position 3 would be considerably greater and thus lead to the observed hydride attack at position 4 producing only the trans-2-alkoxy-3-hydroxytetrahydropyran. It has been shown (69) that the reaction of trans-2,3-epoxy-1-methoxycyclohexane with $LiAlH_4$ produces preferentially trans-2-methoxycyclohexanol while with aqueous sodium hydroxide the same epoxide gives selectively 3α-methoxy-1α,2β-cyclohexanediol ((a), Chart 34). The reaction of cis-2,3-epoxy-1-methoxycyclohexane with aqueous sodium hydroxide produces primarily the 3α-methoxy-1α,2β-cyclohexanediol ((b), Chart 34). This selective attack on the epoxide carbon remote from the C-3 methoxy substituent in both cis and trans



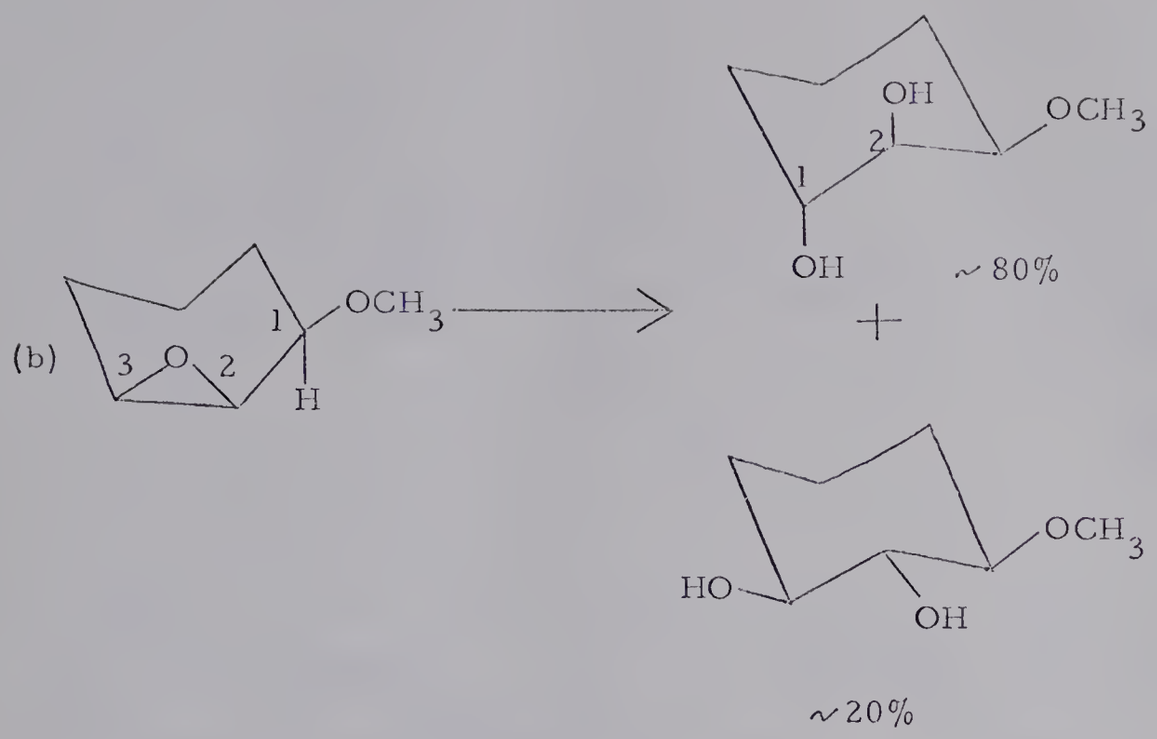
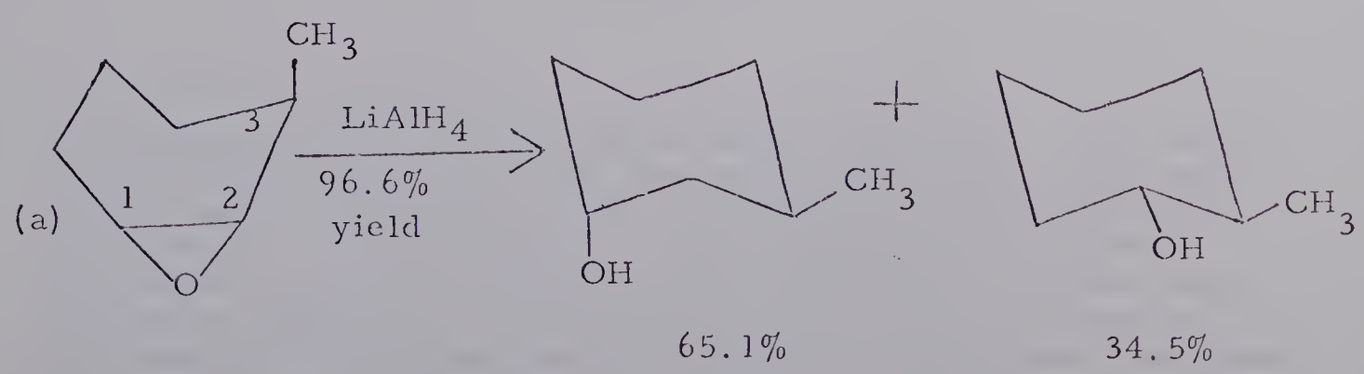


CHART 34

isomers was considered to be due to the inductive effect of the C-3 alkoxy group directing the course of ring opening (69). But the presence as well of a steric effect was thought to be likely in the case of trans-2,3-epoxy-1-methylcyclohexane (69).

Recently, Kavadias (64) studied the reaction of $LiAlH_4$ with 3-substituted cyclohexene oxides in considerable detail*. The results of these experiments are summarized in Chart 35.



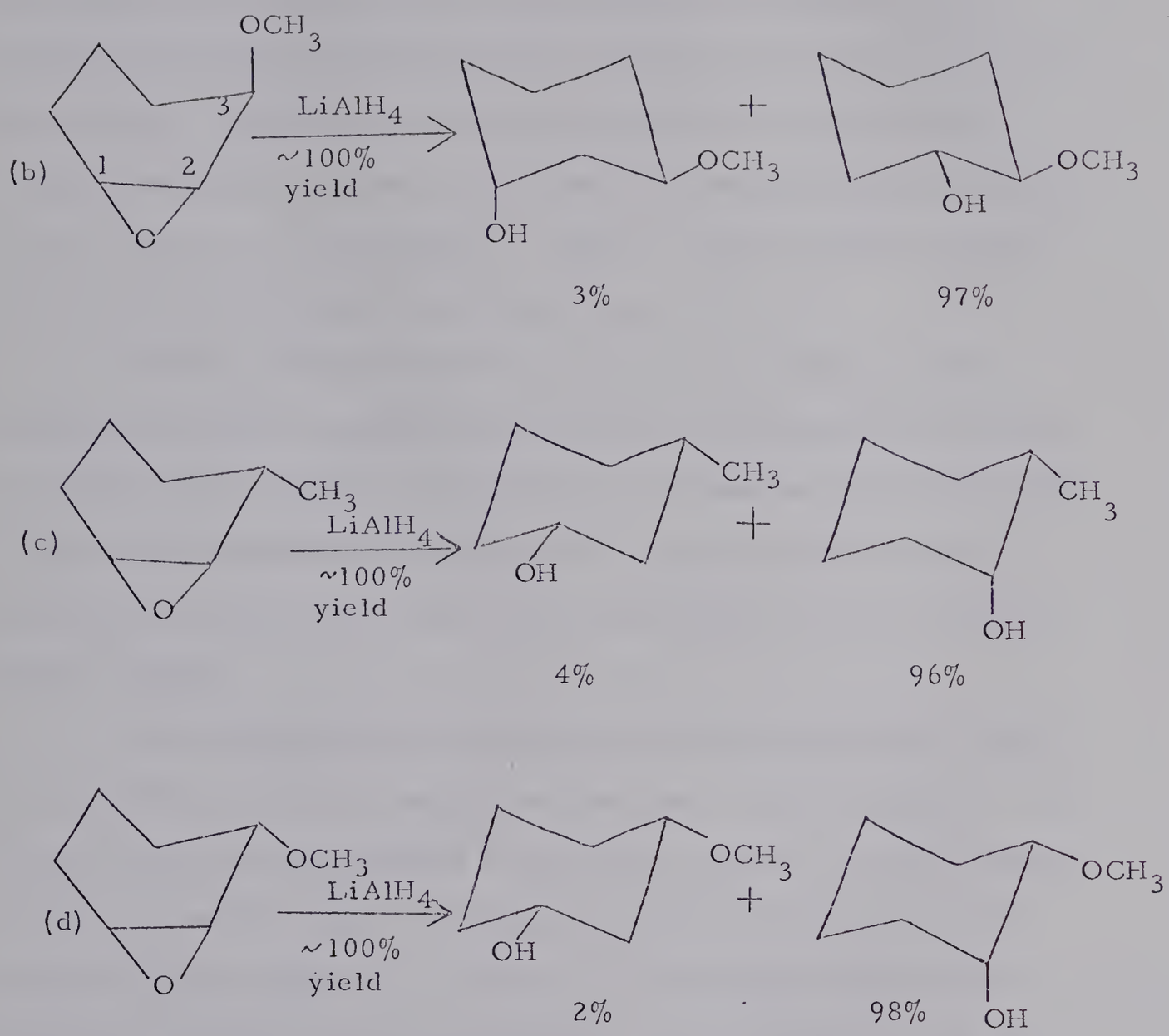


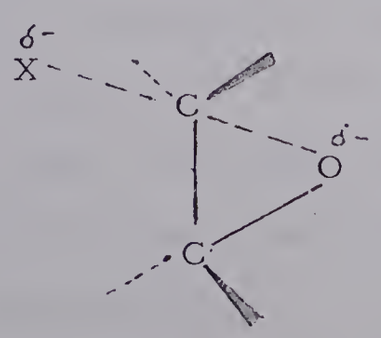
CHART 35

* It is important to point out that Kavadias' work (64), which to the present time has not found its way to the literature, was brought to this author's attention at the commencement of the writing of this thesis. The investigative similarities that exist between Kavadias' work on cyclohexene oxides (64) and the present work on pyranyl epoxides, and in particular the mutual consistancy of the results, is very interesting. However, the present work was in no way generated, directed or influenced by Kavadias' investigations.

Thus far, the term "steric effect" has been used to describe a non-bonded interaction between ring substituents and nucleophilic species attacking an epoxide function on the cyclohexane or tetrahydropyran ring. Used in this sense, the concept of steric hindrance means that approach to the reactive site on the molecule is prevented by the bulk of a ring substituent. However, steric effects can show their influence in a somewhat different way.

Kavadias (64) discussed the role of steric effects in determining the relative stability of the possible transition states involved in epoxide ring opening in 3-substituted cyclohexene oxides (Chart 35). This concept satisfactorily explained the results obtained when 3-substituted cyclohexene oxides were treated with a variety of nucleophilic reagents.

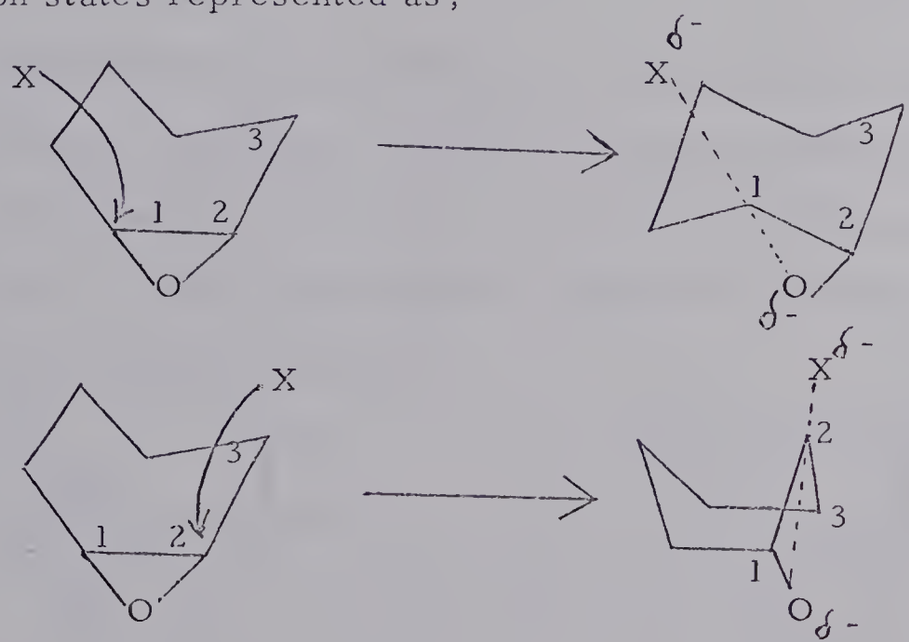
Accumulated evidence (16) has shown that nucleophilic attack on epoxides proceeds by an S_N2 reaction under usual conditions. It is generally accepted (70) that in S_N2 type reactions, in the transition state, the entering group, leaving group and carbon atom on which substitution takes place are colinear. It therefore follows that in opening of epoxide rings by nucleophiles, in the transition state the epoxide oxygen, the nucleophile and site of reaction are colinear,



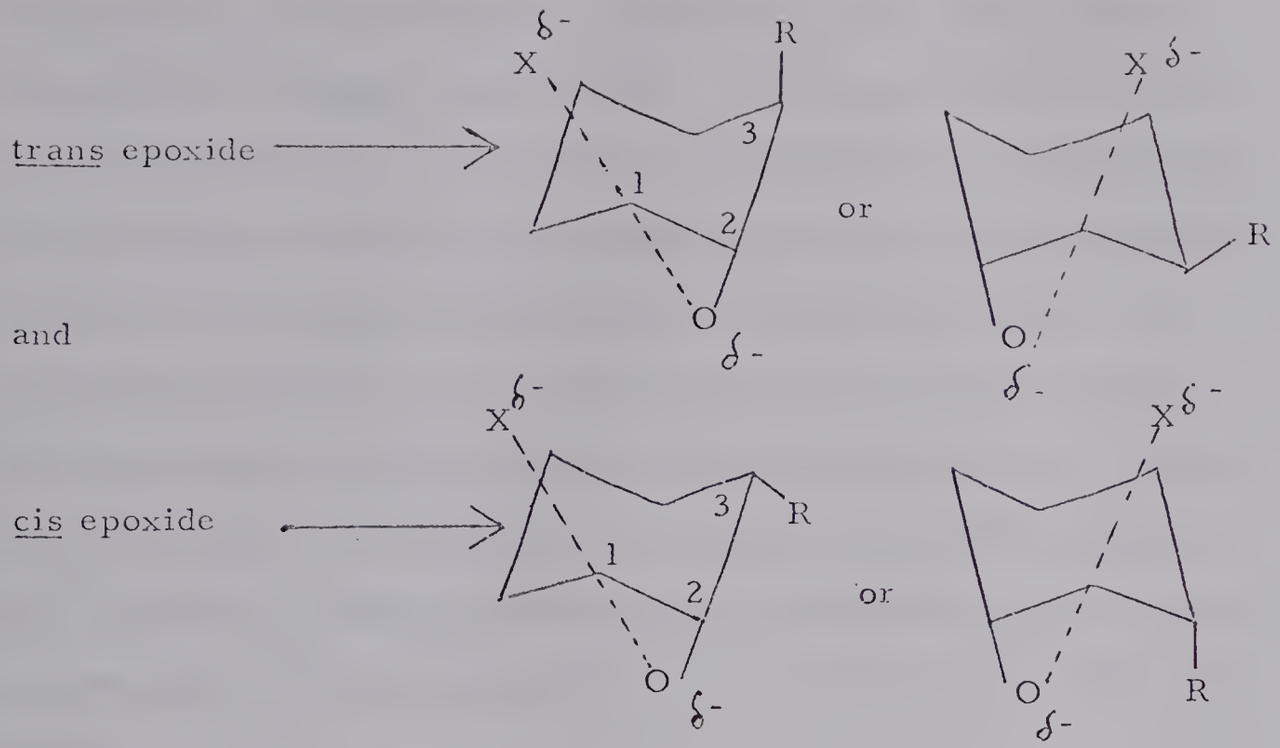
Applying the principles outlined above Kavadias (64) rationalized the preferential attack by $LiAlH_4$ at the 1-position in 3-substituted cyclohexene oxides (Chart 35) in the following way. In cyclohexene oxide two equivalent half-chair conformations can exist in equilibrium,



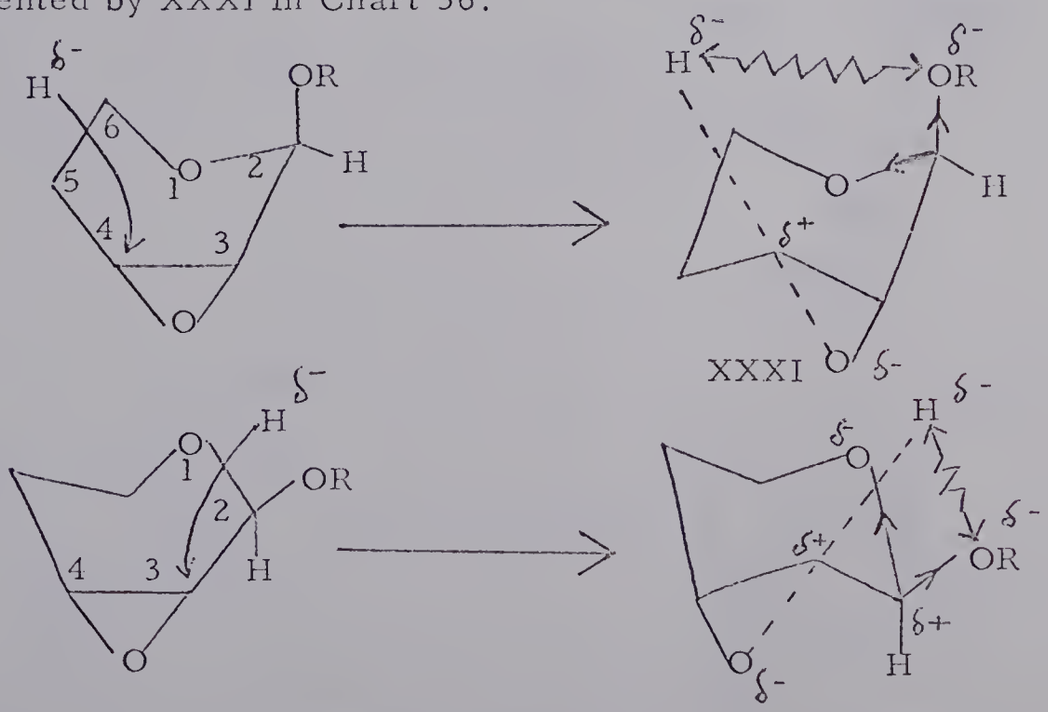
With respect to the left-hand structure, attack by a nucleophile at positions 1 and 2 in each case results in two geometrically different transition states represented as,



On accepted stereochemical grounds the chair-transition state is expected to be more stable and therefore more easily formed than is the boat-transition state. Now with a substituent at the C-3 position two chair-transition states for each of the trans and cis cyclohexene oxides can be written,



Applying the above considerations to the present reaction of $LiAlH_4$ with cis- and trans-2-alkoxy-3,4-epoxytetrahydropyrans leads to the following conclusions. Attack by $LiAlH_4$ (symbolized as $H^{\delta-}$) at C-4 in the trans-epoxide leads to the transition state represented by XXXI in Chart 36.

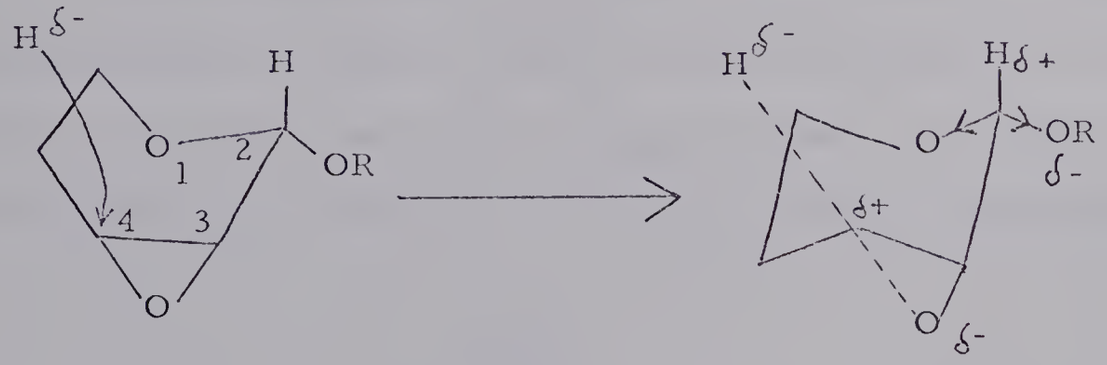


$R = CH_3, t\text{-}C_4H_9$

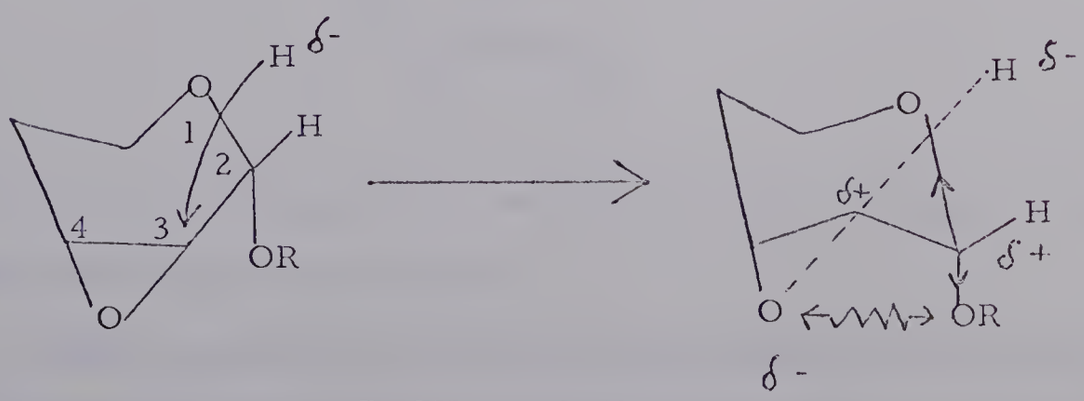
CHART 36

The geometry of this transition state (XXXI) places the 2-alkoxy substituent in a quasi-axial position. This results in a 1,3-diaxial interaction between the incoming nucleophile and the 2-alkoxy group. On the other hand the transition state XXXII, resulting from hydride attack on C-3, appears to be far less favorable than XXXI. In XXXII the nucleophile and the alkoxy group are strongly eclipsed. Such steric interaction would no doubt be greater than a 1,3-diaxial interaction (64). As well there may be an electrostatic repulsion ($H^{\delta-} \leftrightarrow O^{\delta-}$) between the incoming nucleophile and the 2-alkoxy oxygen atom. This would further favor transition state XXXI over XXXII.

For reduction of cis-2-alkoxy-3,4-epoxytetrahydropyran, two transition states XXXIII and XXXIV are possible, as shown in Chart 37. In transition state XXXIII, resulting from hydride attack



XXXIII



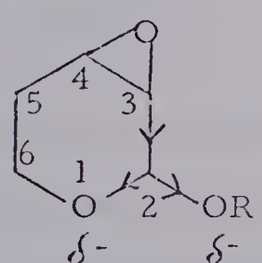
R=CH_3, t-C_4H_9 XXXIV

CHART 37

on C-4, there are obviously no unfavorable nucleophile-substituent interactions. However, as seen from structure XXXIV, which represents attack by hydride at C-3, the 2-alkoxy group in the axial arrangement is very close to the emerging oxygen anion. Therefore, transition state XXXIII is expected to be the more favorable one.

Inductive effects as well may be responsible for preferential attack by $LiAlH_4$ at C-4 in cis- and trans-2-alkoxy-3,4-epoxytetrahydropyrans. It is known (71) that electron-withdrawing and electron-releasing groups have a definite effect on the reactivity of compounds undergoing S_N2 reactions. And generally electron-withdrawing groups decrease the S_N2 reactivity when such groups are located on the carbon atom adjacent to the reactive center.

As the electron-attracting group is located further from the site of reaction its effect on the S_N2 reactivity greatly declines (71). Therefore, in the case of cis- and trans-2-alkoxy-3,4-epoxytetrahydropyrans S_N2 reactivity (i.e. attack by $LiAlH_4$) is expected to be



much less at C-3 than at C-4, resulting from the strongly electron withdrawing oxygen atoms on C-2.

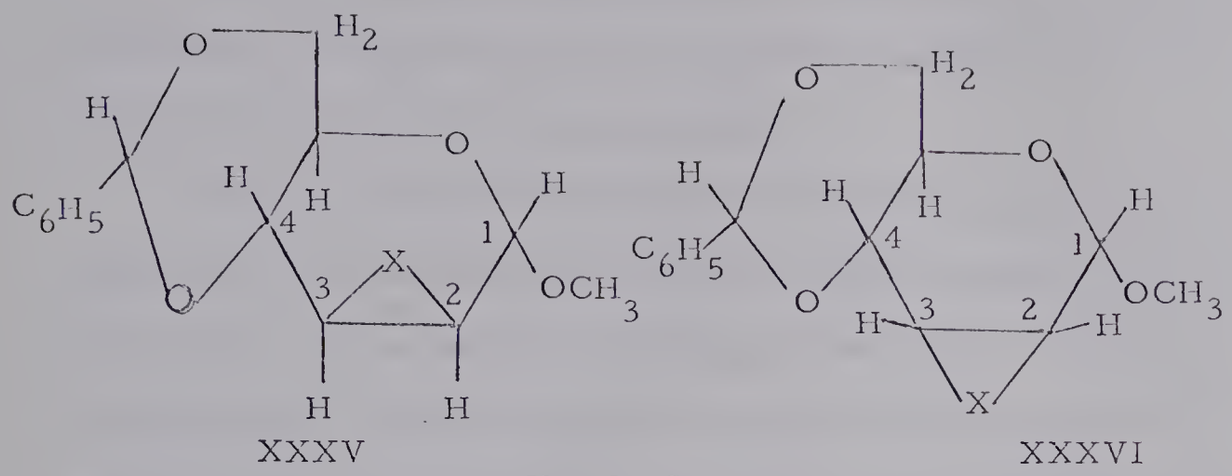
Referring again to transition states XXXI and XXXII (Chart 36) and XXXIII and XXXIV (Chart 37) if stabilization of an incipient

positive charge (represented here as $-C^{\delta+}-$) is most important here then structure XXXI is preferred to XXXII, and XXXIII is preferred to XXXIV. Thus, both stereochemical and electronic considerations favor the same transition states. At present there is no quantitative method of evaluating the individual contributions by stereochemical and electronic factors, discussed above, to determine which is more important in accounting for the observed highly selective attack by hydride at C-4 in these epoxides. It seems reasonable, however, that some combination of these factors determines the direction of epoxide-ring opening.

The present author is inclined to agree with the current view (16) that in 2,3-anhydropentopyranosides, of which the pyranyl epoxides discussed above are analogs, preferred nucleophilic attack at the carbon remote from the anomeric center is determined mainly by electronic factors.

C. 2-Alkoxy-3,4-epoxytetrahydropyrans as models for the assignment of the chemical shifts for protons on the epoxide ring of 2,3-anhydroglycopyranosides.

A recent paper (72) has reported nuclear magnetic resonance data of a number of glycopyranosides each of which contained a 2,3-epoxy, 2,3-episulfide or 2,3-epimine function (Chart 38, XXXV and XXXVI. A relationship was found between the H-1, H-2 coupling constant (as shown in the signal for the anomeric proton) and the cis or trans orientation of the anomeric alkoxy group and the C-2, C-3 epi function. In all cases presented, when these two groups were



X = O, S, NH, NHAc

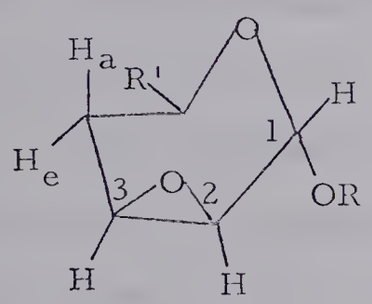
CHART 38

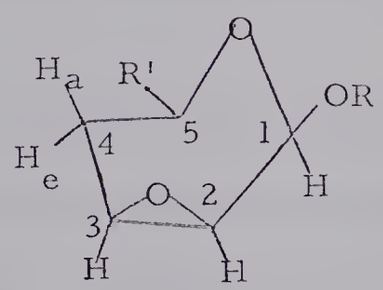
trans, the H-1, H-2 coupling was very small ($J_{1,2} \sim 0$), whereas when they were in the cis arrangement, the H-1, H-2 coupling was 2.5 to 4.5 Hz. This useful information has permitted an assignment of the signals for the C-3 methylene protons in indene oxide and has simplified the analysis of the nuclear magnetic resonance spectra of a variety of cyclopentene oxides (72).

Since it was found that $J_{1,2} = J_{3,4} \sim 0$ for XXXV (X=O), no assignment could be made on this basis as to the signal position of H-2 and H-3 (72). However, by a comparison of the n.m.r. spectra of XXXVI (X=O) and XXXV (X=O) an assignment was apparently possible (72) although the rationale for this is obscure. The signals for the H-3 and H-2 protons of XXXV (X=O) were reported to be at τ7.25 and τ6.93 respectively. Assignments of the H-2 and H-3 signal positions of the analogues of XXXV (Chart 38) were then made by analogy (72).

The 2,3-epoxytetrahydropyrans* discussed in section A of this chapter now prove to be well-suited to the study of the n.m.r. spectra of the 2,3-anhydropyranosides.

In these compounds (XXXVII to XXXXIX, Chart 39)** the signals for the protons on C-4 are well upfield and separated from those of the protons on the remaining carbon atoms. This simplifies the assignment of signals and the problem of their separation, contrary to the situation prevailing in the 2,3-anhydropyranosides which possess an oxygen atom attached to each carbon. Moreover,





XXXVIIa R = CH_3; R' = H

XXXVIII R = t-C_4H_9; R' = H

XXXIX R = CH_3; R' = CH_2-OCH_3

XXVIIb R = CH_3; R' = H

CHART 39

it is highly unlikely that $J_{1,2} \approx J_{3,4a} \approx J_{3,4e} \approx 0$, a condition which would make the assignment of the signals for H-2 and H-3 more

* The positions 3 and 4 in pyrans correspond to 2 and 3 in pyranosides. However for convenience in comparing the n.m.r. data of the sugars with the pyranyl analogs, the carbohydrate convention is adopted in this section.

** The preparation of methyl 2,3-anhydro-4-deoxy-6-O-methyl-α-DL-xylo-pyranoside (XXXIX) is described in Chapter VII.

difficult as in the case of XXXV (72). A further advantage of these models is that the problem of virtual coupling (49, 73) possibly affecting the magnitude of $J_{1,2}$ is eliminated.

The n.m.r. spectra of compounds XXXVII to XXXIX are shown in Figs. 7-10 and the significant τ and J values are listed in Table V. For compounds XXXVIIa, XXXVIII and XXXIX, wherein H-1 and H-2 are trans, two characteristic signals are observed. The anomeric proton appears as a singlet ($J_{1,2} \sim 0$) in the region τ4.88 to τ5.22. A doublet (J = 4.0 Hz)* is observed at τ7.06-τ7.13. These results are similar to those reported (72). Decoupling experiments clearly show the latter doublet to be due to H-2, not H-3.

When the doublet at τ 7.1 was irradiated, the complex (XXXIX) pattern at $\sim\tau$ 6.7 simplified to a quartet but no change was observed in the region τ 7.9 - τ8.2 (H-4a, H-4e). Irradiation at τ 6.7 caused the doublet at τ 7.1 to collapse to a singlet and the development of a simpler pattern at τ 7.9 - τ 8.2. Irradiation at τ 8.13 gave no change in the doublet at τ 7.10 but collapse occurred in the signals at τ 6.7. This information shows that the signal for H-2 is that at τ 7.1 ($J_{2,3}$ = 4.0 Hz) while that for H-3 is at somewhat lower field (see Table V).

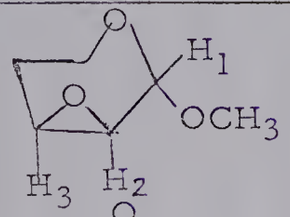
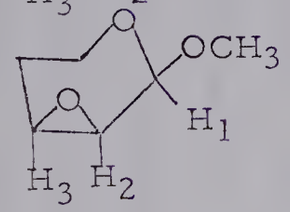
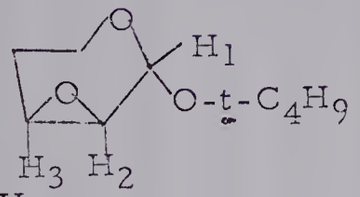
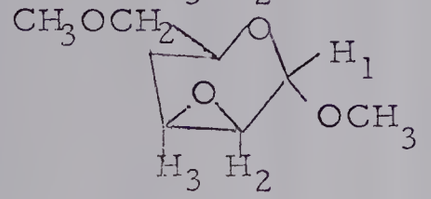
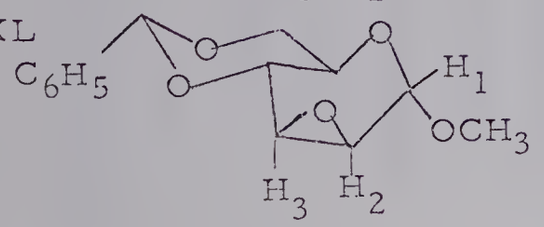
The close similarity of these model compounds to the 2,3-

* The practically constant value of 4.0 Hz for $J_{2,3}$ in compounds XXXVIIa, XXXVIII and XXXIX should be compared to the range of $J_{2,3}$ of 3.8-4.5 Hz found for analogous pyranosides (72). The effect of virtual coupling on the observed chemical shift of H-3 may be responsible for this reported (72) variation.

TABLE V

Observed Chemical Shifts (τ) and First Order Coupling Constants

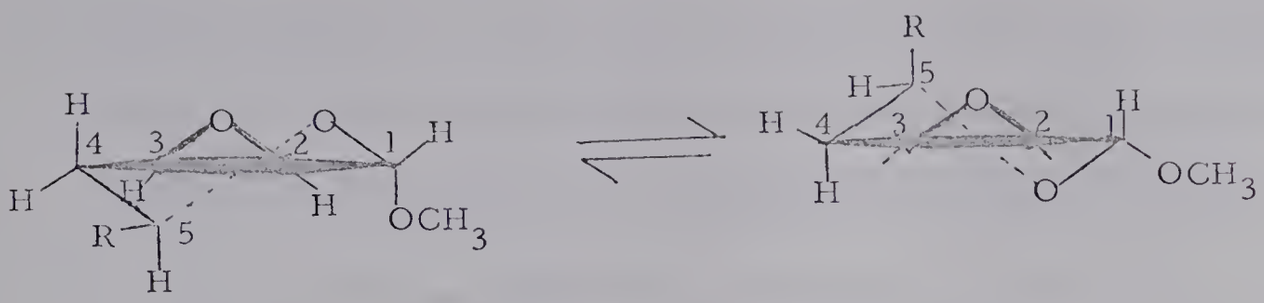
in Cis- and Trans-2-alkoxy-3,4-epoxytetrahydropyrans.

Compound		τ H-1	$J_{1,2}$ Hz	τ H-2	τ H-3	$J_{2,3}$ Hz	Fig.
XXXVIIa		5.22	0	7.04	6.71	4.0	7,8
XXXVIIb		5.15	2.5	6.72	~6.58	4.0	7,9
XXXVIII		4.88	0	7.13	6.74	4.0	10
XXXIX		5.18	0	7.10	6.74	4.0	11
XL		5.14	0	6.88	6.56	3.8	12

epipyranosides clearly indicates that the reported signal assignments for H-2 and H-3 (72) should be reversed. Further support for this is found in the n.m.r. spectrum (Fig. 12) of methyl 4,6-O-benzylidene-2,3-anhydro-α-D-mannopyranoside, XL*. Significant signal assignments of XL are shown in Table V and in Fig. 12. Irradiation at τ6.56 (H-3) caused the doublet at τ 6.88 (H-2) to collapse to a singlet as well as a sharpening of the signals at τ 5.75 (H-4). Irradiation at τ 5.75 (H-4) caused a sharpening of the signal at τ6.56 (H-3) and a marked collapse of the multiplet at τ6.30 (H-5) but no change in the doublet at τ 6.88 (H-2).

The conformational implications of the information in Table V are interesting. The benzylidene group provides methyl 4,6-O-benzylidene-2,3-anhydro-α-D-mannopyranoside with a greater degree of rigidity than is found in the epoxytetrahydropyrans XXXVII and XXXVIII. The methoxymethyl group of XXXIX would no doubt result in the existence of XXXIX largely in the conformer in which the methoxymethyl group is equatorial. Models show that XXXVII and XXXVIII possess considerable conformational freedom between the two extremes shown below. Such mobility is associated with rotation about the C-1, C-2 and C-3, C-4 bonds with consequent change in the dihedral angle, coupling constant and signal position (chemical shift) of the protons concerned. No doubt the values observed are time-averaged. Yet in all cases, for XXXVIIa,

* Methyl 4,6-O-benzylidene-2,3-anhydro-α-D-mannopyranoside was prepared in this laboratory by Dr. Moheshwar Sharma according to a known procedure (74).



XXXVIII, and XXXIX, the couplings $J_{1,2}{\sim}0$ and $J_{2,3} = 4.0$ Hz indicate a marked similarity of their conformational equilibria.

V. STEREOCHEMICAL VS POLAR CONTROL IN THE PREPARATION AND TREATMENT WITH ETHANOLIC SODIUM ETHOXIDE OF THE ISOMERIC-3,4-DIBROMO-2-ETHOXYTETRAHYDROPYRANS.

Woods and Temin (75) have reported the preparation of a diethoxytetrahydropyran, but its structure was not definitely established. Since the work for this thesis involved preparation of oxygen-substituted tetrahydropyrans, it seemed reasonable to reinvestigate Woods and Temin's work, and to determine whether it had merit in relation to the present problem.

The reaction of hot ethanolic potassium hydroxide with an isomeric mixture of 3,4-dibromo-2-ethoxytetrahydropyrans (XLIIa and XLIIb, Chart 40)(75) produced, in poor yield (ca. 16%), a mixture of 3-bromo-2-ethoxy-5,6-dihydro-2H-pyran (XLIII) and a compound suggested to be 2,4-diethoxy-5,6-dihydro-2H-pyran (XLIV). Their assignment of the structure of the latter compound was based on findings that catalytic hydrogenation of XLIV gave a diethoxytetrahydropyran, XLV*, (evidence for one double bond in XLIV), and that acid hydrolysis of XLIV followed by phenylhydrazone formation gave a substance which contained one ethoxy group.

In view of the ease with which vinyl ethers are hydrolyzed under acidic conditions (76, 77), it is expected that XLIV would cleave not only at the acetal function but also at the vinyl ether linkage

* The structure of XLIII and XLV were also not definitely established (75).

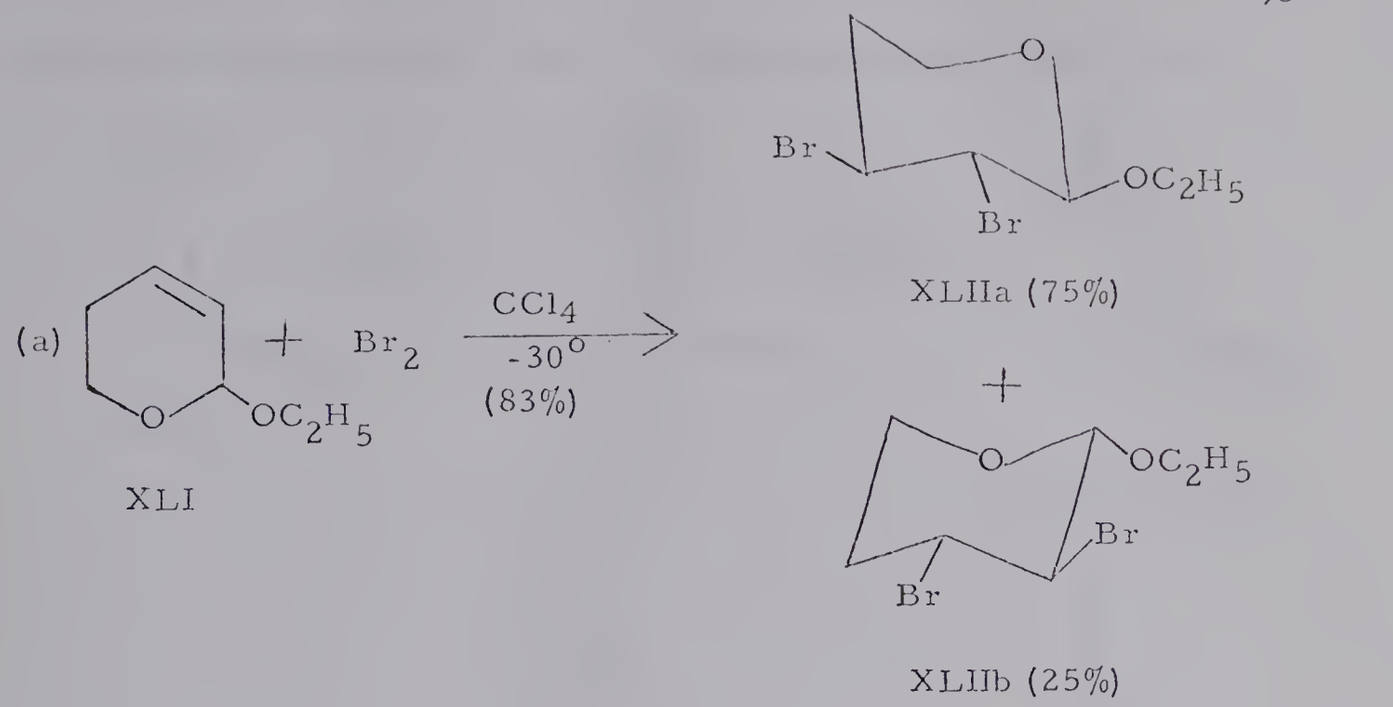
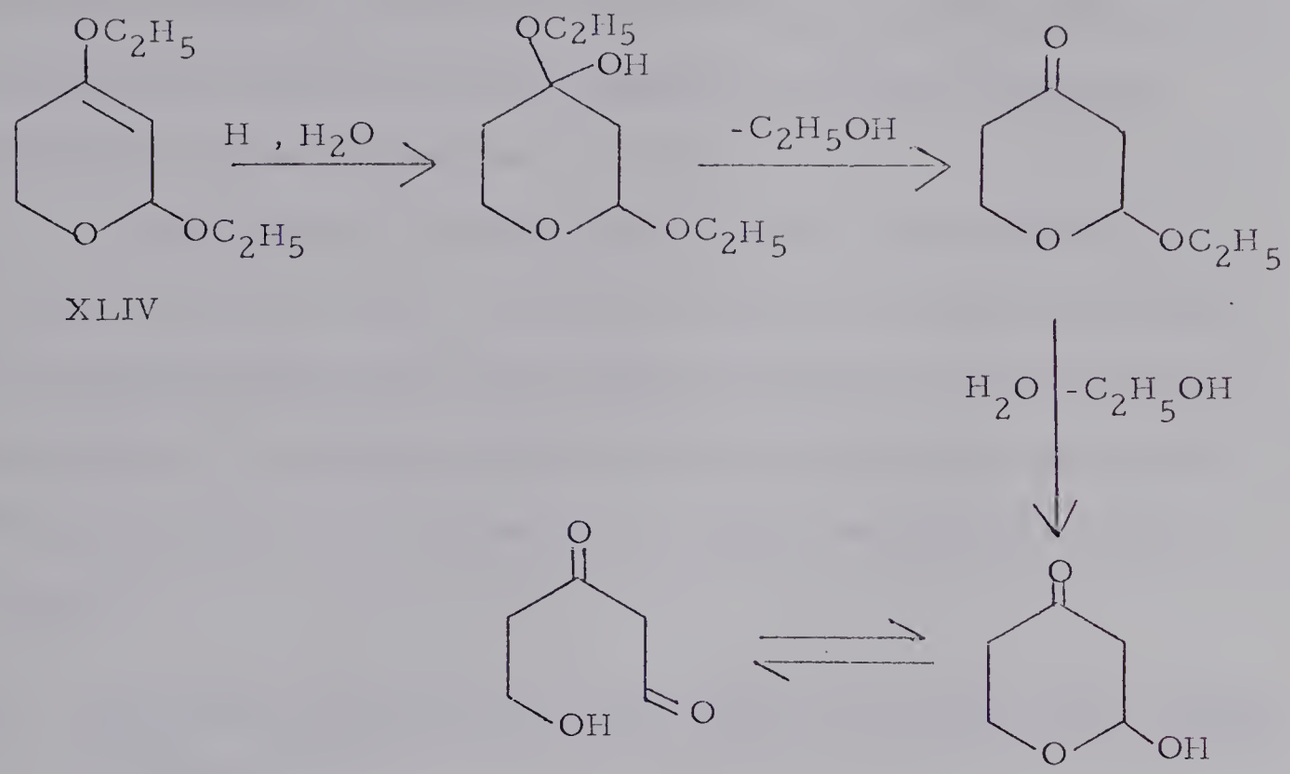

(a)
Br2
CCl4
-30°
(83%)
XLI
XLIIa (75%)
XLIIb (25%)
(b) XLIIa and b
KOH, C2H5OH
Hot
XLIII
XLIV
H2/Pd-C
H2/Pd-C
XLV

CHART 40

with loss of both ethoxy groups. Hence, structure XLIV is not



consistent with the hydrolysis data presented (75). It is also known that 1,2-dibromocyclohexane, treated with alcoholic base is converted almost entirely to 3-ethoxycyclohexane (78). Accordingly, on this basis, 3,4-dibromo-2-ethoxytetrahydropyran (XLIIa and b) under similar conditions might be expected to give one or more of the α, β-unsaturated ethers XLVI, XLVII or XLVIII (Chart 41).

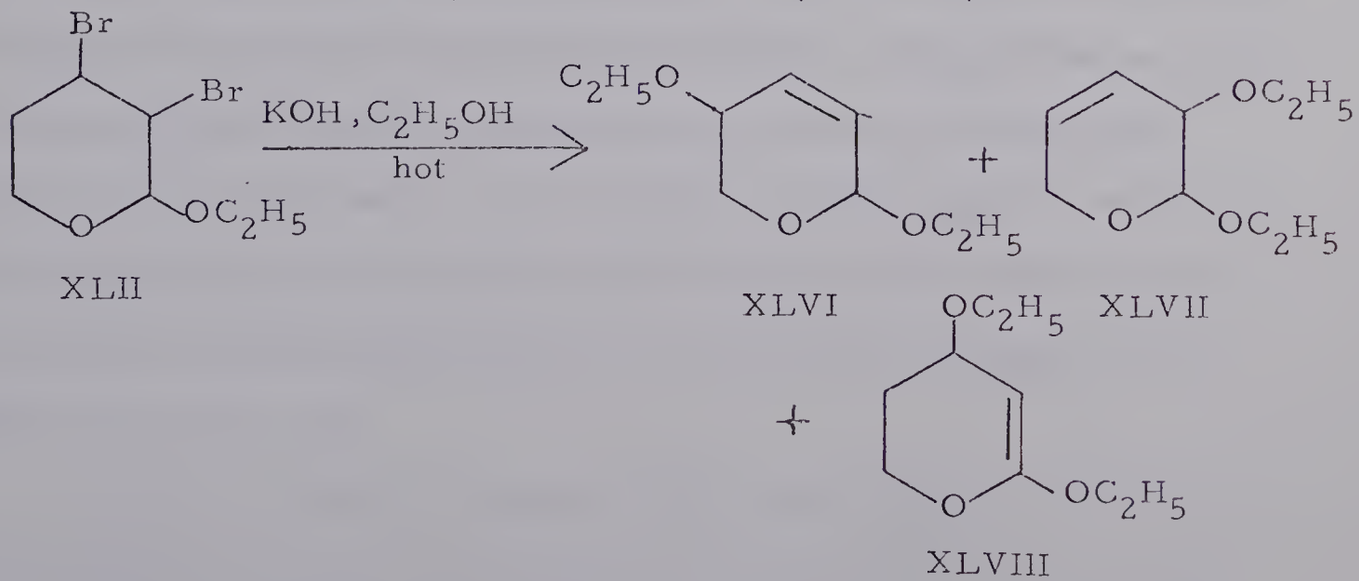


CHART 41

In view of the observation (79) that the proton on the dioxy carbon of α-bromoacetals is difficult to remove by use of ordinary bases, the likelihood that XLVIII is formed seems to be small, though the possibility cannot be ruled out.

The following discussion describes the reinvestigation of Woods and Temin's work. The aim was to elucidate the structure of compounds obtained by these authors and thus to resolve the above anomalies. As well it was desirable to determine the usefulness of these reactions for the preparation of oxygen substituted tetrahydropyrans.

A. Preparation and structure of the isomeric 3,4-dibromo-2-ethoxytetrahydropyrans.

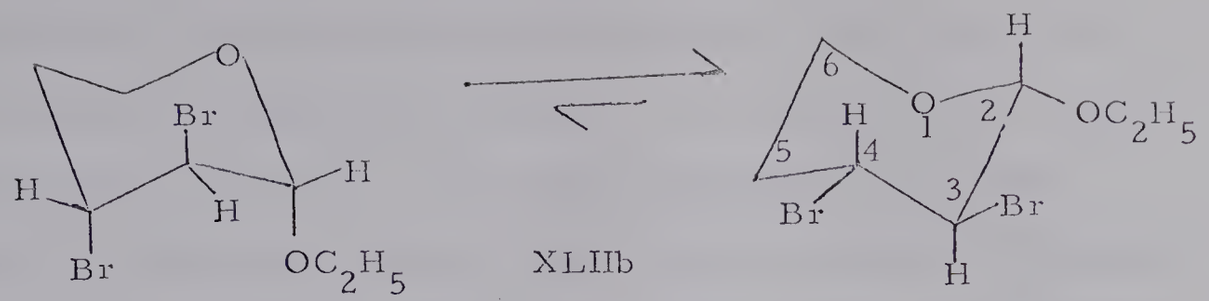
Bromination of 2-ethoxy-5,6-dihydro-2H-pyran (XLI) by a modification of the published procedure (75) was carried out and gave an 83% yield of a 3:1 mixture of two isomeric dibromides, in agreement with the reported results (75). The minor constituent, a solid, was readily separated by crystallization, while the major constituent, a liquid, was purified by fractional distillation. The physical properties of the individual isomers agreed with the literature values (75). Both isomeric dibromides were considered to be trans dibromides in view of the accumulated evidence that bromination of olefins such as cyclohexene gives predominantly, if not entirely, the trans vicinal dibromides (36, 80).

The 3:1 mixture of isomeric dibromides did not arise from an equilibration process, stemming from isomerization at the acetal

linkage. This was shown by the absence of evidence of such isomerization when either isomer was allowed to stand at room temperature for 24 hours in absolute ethanol containing a catalytic amount of p-toluenesulfonic acid. Only when these solutions were heated under reflux for 12 hours did isomerization occur, and then merely to the extent of 5-10%*. It is thus clear that under the low temperature conditions employed for the bromination (-35° to -30°) and the relatively short reaction time (1-2 h), no perceptible isomerization could have occurred. Therefore, the 3:1 ratio of isomers is the direct result of selective bromination.

The configuration and conformation of the solid isomer was examined by n.m.r. spectroscopy. The spectrum (Fig. 13), obtained in $CDCl_3$ (tetramethylsilane as reference), showed the anomeric proton signal as a doublet centered at τ5.52 ($J_{2,3}$ = 7.0 Hz). In acetonitrile, saturated with tetra-n-butylammonium bromide, the anomeric proton signal position changed to τ5.32 ($J_{2,3}$ = 7.8 Hz). The large coupling, as well as the change observed in the signals when acetonitrile was used as solvent, shows that the ethoxy and bromine substituents located on C-2 and C-3 respectively, are trans, and that the preferred conformation is that in which all substituents are equatorial (Chart 42). This procedure is similar to that employed by Lemieux and Fraser-Reid (37). These workers used the above two solvent systems in order to assign configurations to

* This is in agreement with the observation that these 3,4-dibromo-2-ethoxytetrahydropyrans are unusually stable to acid hydrolysis (75).



axial XLIIb equatorial

CHART 42

cis- and trans-3-bromo-2-methoxytetrahydropyran on the basis of the C-2 H (anomeric proton) signals observed in the n.m.r. spectrum of a mixture of these two isomers. Thus the C-2 H doublet with the larger spacing in $CDCl_3$, which in the acetonitrile (polar)solvent system shifted its position and widened, was assigned to the trans isomer, while the doublet with the smaller spacing which underwent little change in the more polar solvent was due to the cis isomer (37).

Irradiation of the doublet ($J_{2,3}$ = 7.0) at τ5.52 (H-2) of the dibromide XLIIb (Fig. 13) caused collapse of the quartet (of spacings 7.0 Hz and 9.8 Hz) centered at τ6.1 to a doublet of spacing 9.8 Hz. The latter signal is logically due to H-3 since in the favored ("equatorial") conformation of XLIIb (Chart 42) this proton is trans diaxial to H-2 and H-4, therefore $J_{2,3}$ and $J_{3,4}$ is expected to be large.

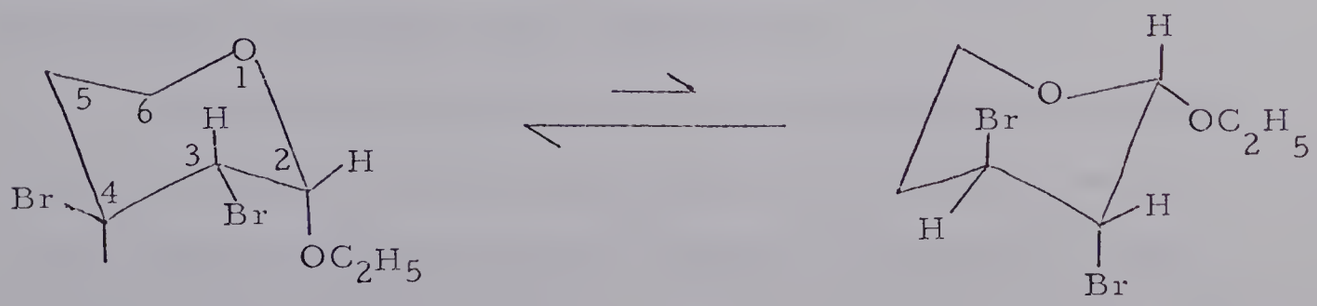
Irradiation at τ6.10 caused the doublet due to H-2 at τ5.52 to collapse to a singlet while the multiplet centered at τ5.8 simplified to a quartet with spacings 9.8 Hz and 5.0Hz. These spacings are most likely due to the H-4, H-5 axial ($J_{4,5'}$) and H-4, H-5 equatorial couplings respectively in the spectrum of H-4. Irradiation at τ5.81 resulted in collapse of the quartet at τ6.10 to a doublet of spacing 7.0 Hz.

On the basis of the decoupling information the chemical shifts

for H-2, H-3 and H-4 are respectively τ5.52, τ6.1 and τ5.8. The appropriate couplings are $J_{2,3}$ = 7.0 Hz, $J_{3,4}$ = 9.8 Hz, $J_{4,5'}$ = 9.8 Hz and $J_{4,5}$ = 5.0 Hz. The large coupling $J_{3,4} \sim 9.8$ Hz showed by first order analysis clearly indicates that the two bromine atoms in XLIIb on C-3 and C-4 are in the trans diequatorial relationship.

The nuclear magnetic resonance spectrum (Fig. 14) of the liquid isomer in $CDCl_3$ showed a doublet for the anomeric proton at τ5.12 ($J_{2,3}$ = 2.8 Hz) which was practically the same as that obtained in acetonitrile saturated with tetra-n-butylammonium bromide (τ5.10; $J_{2,3}$ = 2.8 Hz). These values agree with the structural assignment of the liquid isomer as XLIIa (Chart 43), but offer no information concerning the preferred conformation.

By irradiation at τ5.12 (the signal for the anomeric proton on C-2), the quartet centered at τ5.89 in the 100 MHz spectrum (Fig. 14) collapsed to a doublet ($J_{3,4}$ = 10 Hz) showing that the quartet at τ5.89 was due to the C-3 proton. Accordingly, the large coupling (10 Hz) between C-3 H and C-4 H clearly shows that the preferred conformation of XLIIa must be that in which the two bromine atoms



Br-Br diequatorial XLIIa Br-Br diaxial

CHART 43

are diequatorial. This is not surprising since the two Br-O gauche interactions between the C-3 Br and the two C-2 oxygens*, as well as the anomeric effect (discussed in Chapter II, section B) are all expected to favor the Br-Br diequatorial conformation of XLIIa (Chart 43). The n.m.r. information obtained for both XLIIa and XLIIb supports the view that the reaction of 2-ethoxy-5,6-dihydro-2H-pyran with bromine gave trans dibromides.

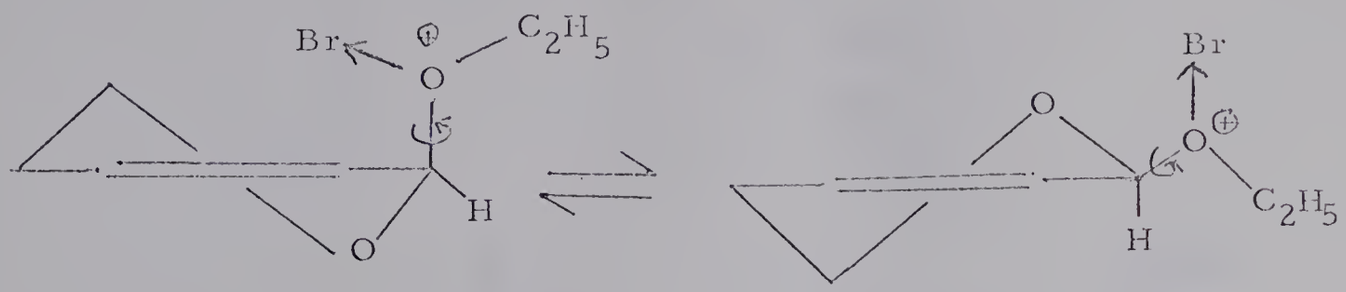
The preferential formation of the liquid isomer 3,4-dibromo-2-ethoxytetrahydropyran XLIIa, deserves some comment. It is known that ethers form complexes with bromine, and also that ether-bromine complexes (82) brominate aromatic hydrocarbons (83, 84) more readily than does molecular bromine alone. This was considered due to assistance by the ether in the formation of the bromonium ion species, which attacked the aromatic ring.

In the reaction of bromine with 2-ethoxy-5,6-dihydro-2H-pyran it is quite possible that bromine-oxygen complex formation might be preferred to that of π complex formation between bromine and the double bond. If this is so, then it is likely that such a complex could provide the $Br^{\oplus}$ species which would attack the pi bond and thus initiate bromination of the double bond.

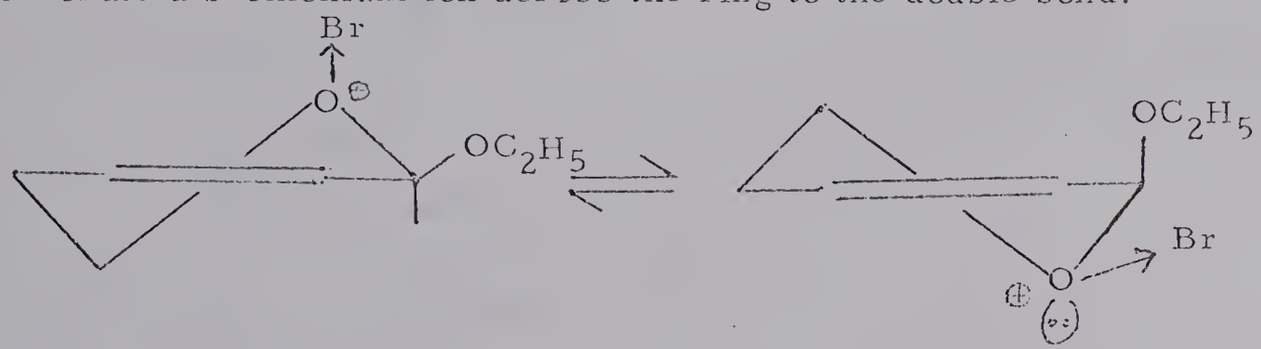
Examination of models shows that a bromine atom attached to the ethoxy oxygen atom is in a geometrically favorable situation to react with the π bond in the same molecule, provided the ethoxy

* In the carbohydrates similar interactions are generally referred to as the Reeves $\Delta 2$ effect (80). Bisection by a C-3 oxygen (C-2 in carbohydrate nomenclature) of the C-2 (anomeric) oxygens is known (80) to be highly unfavorable.

group is in a quasi-axial conformation.



However, a bromine-oxygen complex with the ring oxygen (which is felt to have an equal probability of formation) is not well placed to donate a bromonium ion across the ring to the double bond.



On this basis then the bromonium ion formed from the double bond should be predominantly cis to the neighboring alkoxy group (Chart 44), if bromine-oxygen complexation precedes bromonium ion formation.

Bannard et al (85) have considered the possibility of a similar intervention of a bromine-oxygen complex in directing the reaction of aqueous N-bromosuccinimide with 3-methoxycyclohexene. They have, however, dismissed this on the basis of findings by Henbest and Wilson (86) that addition of hypobromous acid to the steroids 5α-cholest-1-ene and 5α-cholest-1-en-3 β-ol (Chart 45) both gave products in which the bromine was trans to the C-10 methyl group thus suggesting that the C-3 OH did not direct bromine entry via association of $Br^{\oplus}$ with OH. Examination of models of these two

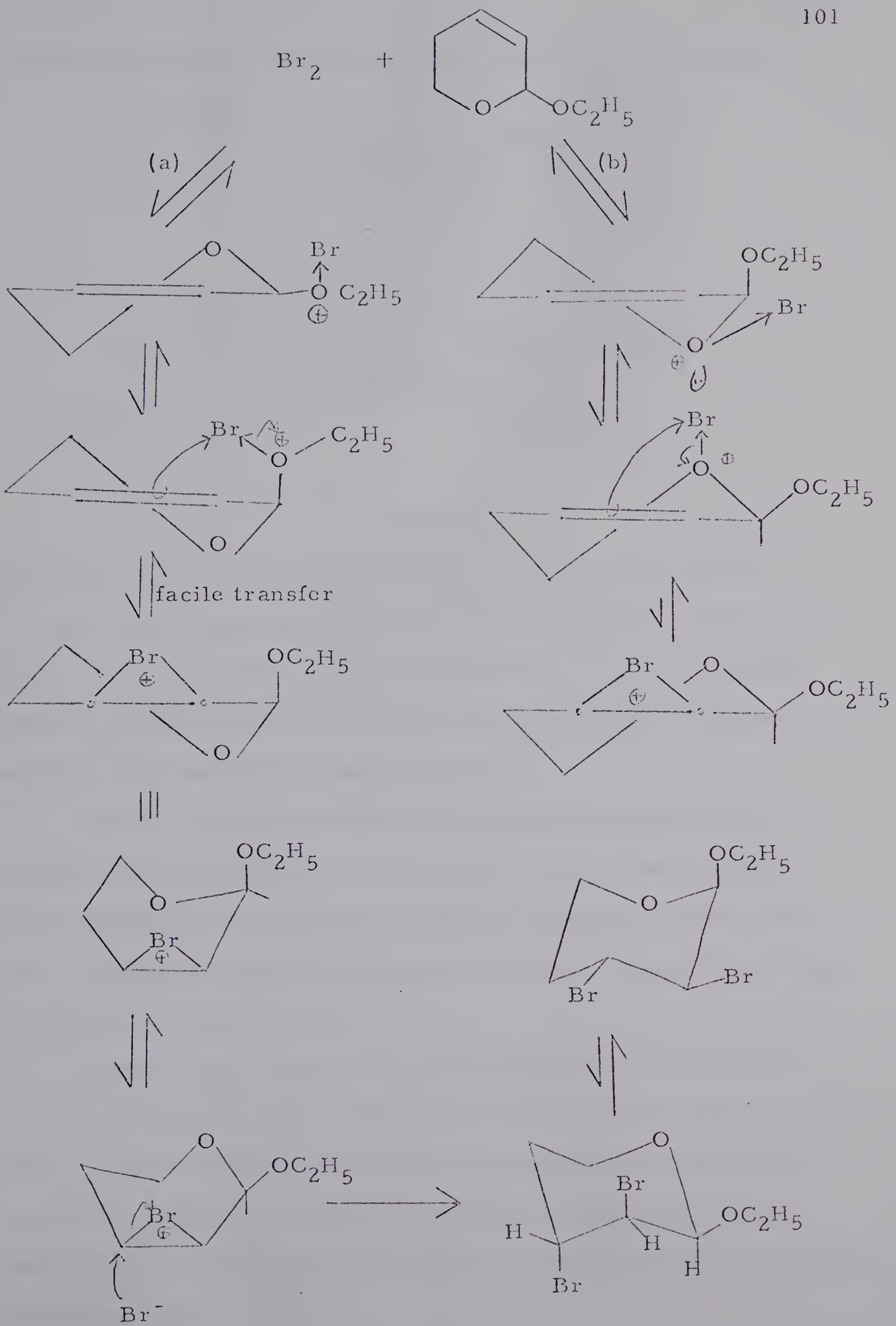


CHART 44

steroids shows quite clearly that even if such a bromine-oxygen

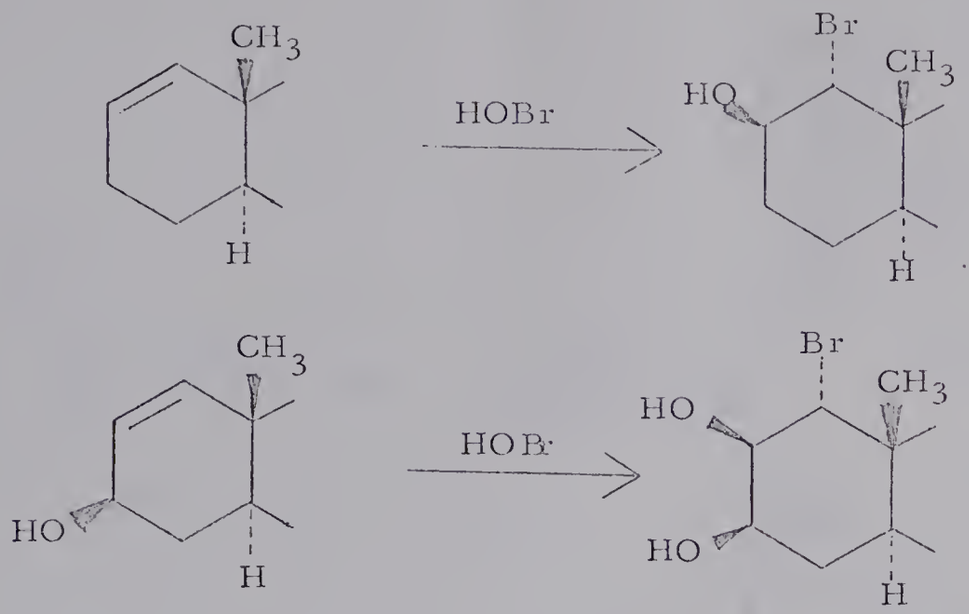


CHART 45

complex had formed, the rigid structure of the steroid molecule was such that the strong steric interaction between the C-10 methyl group and the C-3 hydroxyl prevented formation of a conformer in which the bromine-hydroxyl complex would be favorably situated near the pi bond for such $Br^{\oplus}$ transfer to occur.

It is felt, therefore, that the reported work (86) does not eliminate the possibility of halogen-oxygen complex participation in the bromination of 2-ethoxy-5,6-dihydro-2H-pyran and the hypohalite addition to 3-methoxycyclohexene (85) since both of these ring compounds are quite flexible.

Another case of selectivity in halogenation is described in the work of Kavadias (64). When he treated 3-methoxycyclohexene with an acetic acid mixture of silver acetate and iodine (Prevost reaction) he obtained two isomeric products of which that isomer predominated in which the iodine atom was situated cis to the methoxy group (Chart 46).

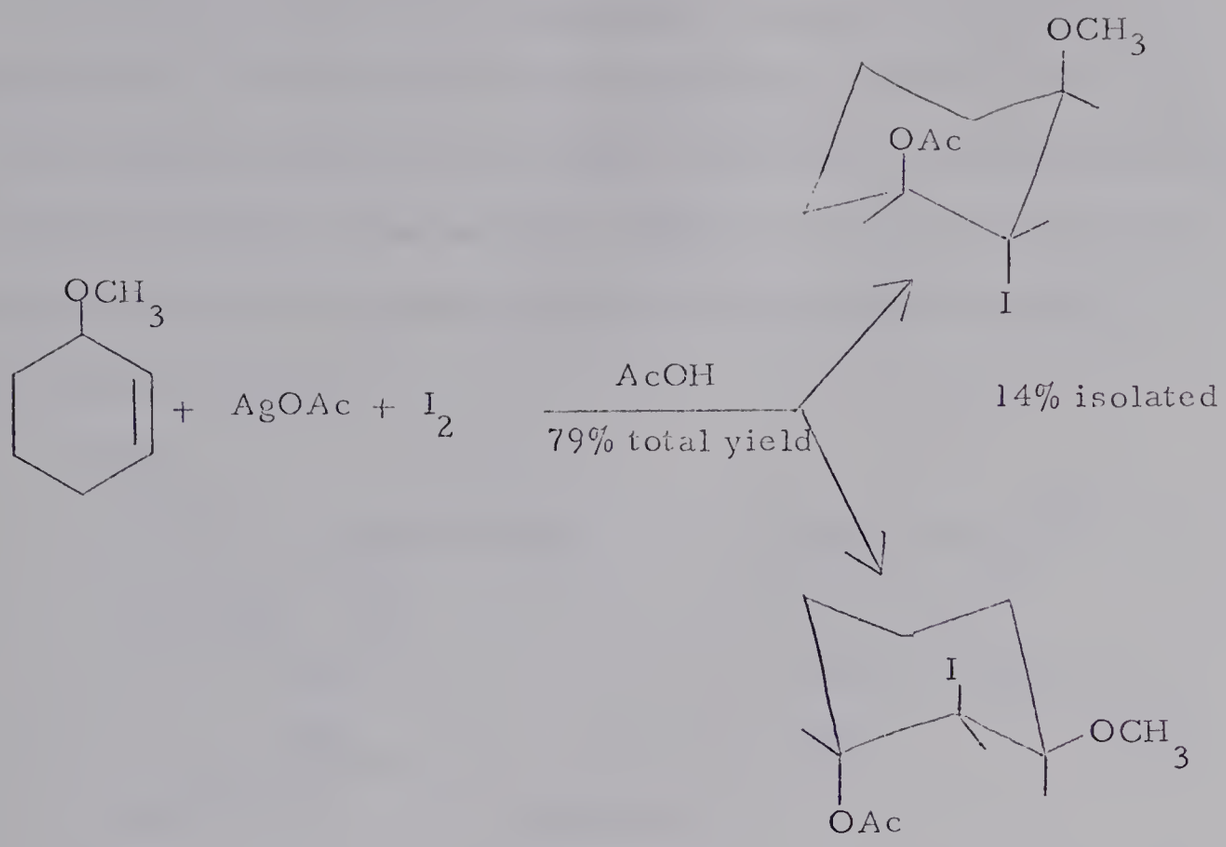
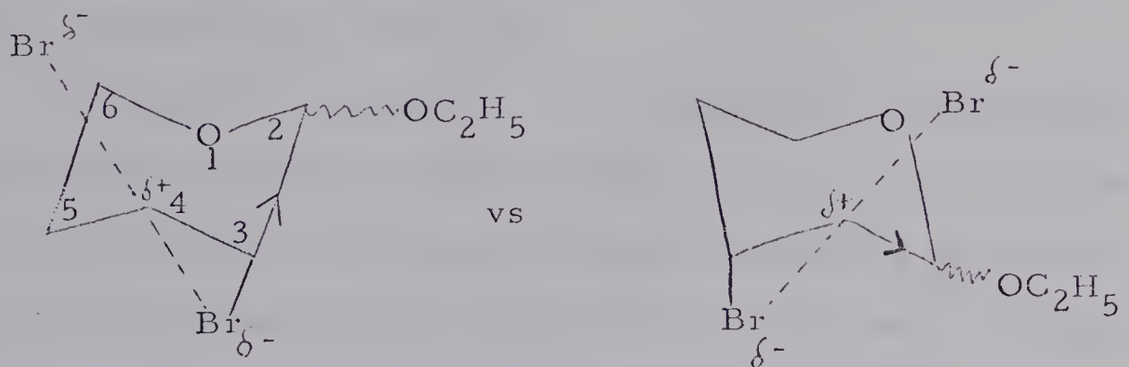


CHART 46

Though Kavadias offered no explanation for the preferred cis-iodination it can be rationalized by arguments similar to those in this thesis advanced to account for the selectivity observed in the bromination of 2-ethoxy-5,6-dihydro-2H-pyran. It is known (64) that the active species in the Prevost reaction is the iodonium ion.

Returning to the steps of bromination of 2-ethoxy-5,6-dihydro-2H-pyran as suggested in Chart 44, when the bromonium ion formed from the olefin is attacked by $Br^{\ominus}$, Br-C bond breaking remote from the C-2 ethoxy group should be preferred (Chart 47). This is thought to be reasonable since the mechanism of the opening of the cyclic bromonium ion by $Br^{\ominus}$ is expected to parallel closely the opening of the analogous epoxide ring in 2-alkoxy-3,4-epoxytetrahydropyrans by $LiAlH_4$ (see Chapter IV, section B).

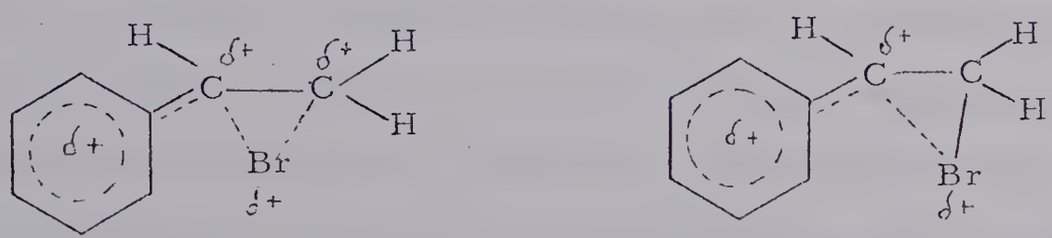
Consideration of the two possible transition states that can play a role in attack by $Br^{\ominus}$ on the bromonium ion (Chart 47) leads to the conclusion that the most stable form is the one involving attack at the 4-position*. The inductive influence of the C-2 dioxy unit is expected to play an important role in the opening of the cyclic bromonium ion by $Br^{\ominus}$.



preferred

CHART 47

Recently, Yates and Wright (87) obtained kinetic and stereochemical evidence for the existence of an "unsymmetrical" bromonium ion (Chart 48), encountered in the bromination of styrene, in the presence of a variety of nucleophiles. These workers concluded



Unsymmetrical styrene bromonium ion of Yates and Wright (87).

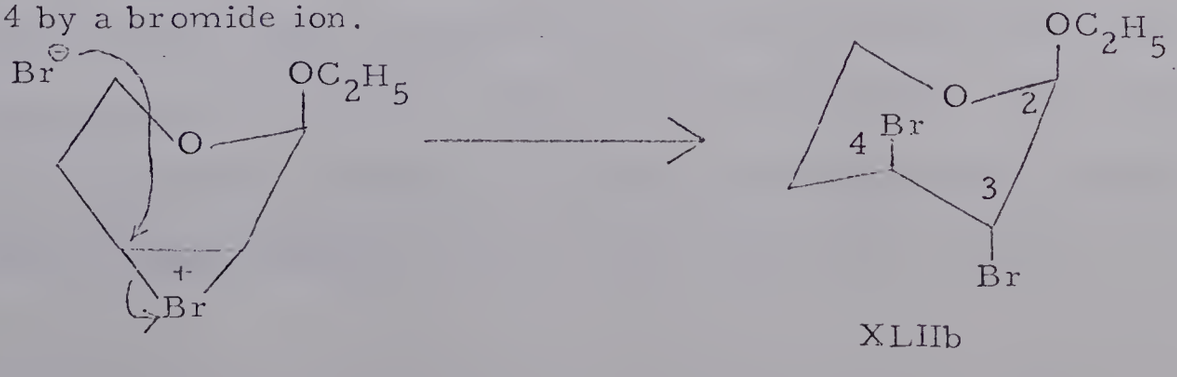
CHART 48

* The factors governing the stabilities of the two transition states possible during opening by $LiAlH_4$ of the epoxide ring, in either cis- or trans-2-alkoxy-3,4-epoxytetrahydropyrans, have been discussed in considerable detail in Chapter IV, section B of this thesis. Opening by Br^- of the cyclic bromonium ion can be viewed as being analogous to nucleophilic attack on an epoxide ring. Hence corresponding transition states relating to bromonium ion and epoxide ring opening should have somewhat similar properties.

from their study that in the bromonium ion intermediate formed during bromination of styrene the C-Br bond to the secondary carbon (i.e. geminal to the phenyl group) is weaker than the C-Br bond to the primary carbon since attack on the bromonium ion occurred almost exclusively at the secondary carbon. Yates and Wright (87) asserted that this was due to the greater stability of the benzyl-like incipient carbonium ion (Chart 48).

In this author's opinion it seems reasonable to assume that due to an inductive effect, caused by the two oxygen atoms attached to C-2, the bromonium ion from 2-ethoxy-5,6-dihydro-2H-pyran has an unsymmetrical nature, and therefore breaks more readily at C-4 than at C-2. This is because a partial positive charge on C-4 would be far less destabilized by the C-2 dioxy function than would a similar charge at C-3 (Chart 47).

In summation then the preferential formation of XLIIa (3,4-dibromo-2-ethoxytetrahydropyran - liquid isomer) from addition of bromine to 2-ethoxy-5,6-dihydro-2H-pyran can be accounted for if it is assumed that a rapidly formed bromine-ethoxy complex donates a bromonium ion to the pi bond, producing a cyclic bromonium ion, which subsequently is exclusively attacked by $Br^{\ominus}$ at the 4-position (Chart 44). Formation of the less abundant all-trans dibromo isomer XLIIb, can occur from a trans bromonium ion which is attacked at C-4 by a bromide ion.



XLIIb

B. Treatment of the isomeric 3,4-dibromo-2-ethoxytetrahydropyrans with ethanolic sodium ethoxide.

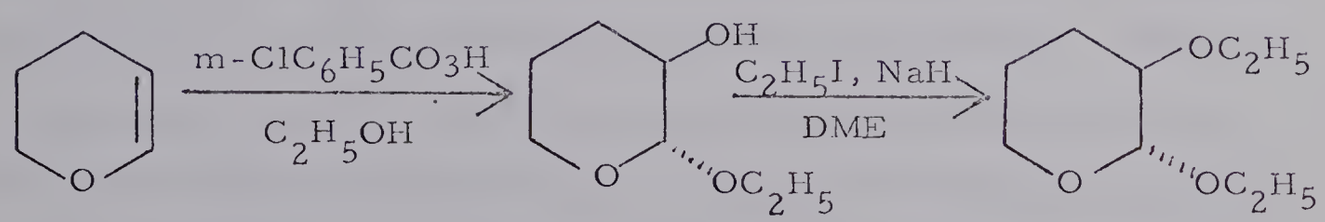
The following discussion describes work done in this laboratory to determine the structure of the product or products obtained when the isomeric 3,4-dibromo-2-ethoxytetrahydropyrans were treated with hot alkaline ethanol.

Treatment of the 3:1 isomeric mixture of ethoxy dibromides, XLIIa and XLIIb (Chart 40), with ethanolic sodium ethoxide, or potassium hydroxide, gave a liquid (~30% yield) which was shown by gas liquid chromatography to be composed of two components in a ratio of 6:1. These were separated by preparative gas-liquid chromatography and each component showed physical characteristics closely similar to those reported (75), for compounds XLIV and XLIII (Chart 40) respectively.

The major component, which proved to be a diethoxy compound (XLIV), showed no absorption in the 1610-1690 cm^{-1} in its infrared spectrum. Absorption in this region would indicate the presence of a vinyl ether group (88, 89) in the pyran ring. No absorption for OH was visible. The nuclear magnetic resonance spectrum in $CDCl_3$ showed a signal which integrated for two olefinic protons and was a multiplet in the region τ 3.9 - 4.5. Thusfar these facts are consistent with either structure XLVI or XLVII (Chart 41) but not with structure XLIV (Chart 40) or XLVIII (Chart 41). The isomers XLIV and XLVIII, if they occur at all, must be present at a level which escapes detection by g.l.c., I.R. and n.m.r. analysis. The

anomeric proton signal appeared as a doublet at τ 5.29 ($J_{2,3}$ = 2.5 Hz). Also, a narrow multiplet was present in the anomeric region centered at τ 5.14 indicative of an impurity (~20%), possibly an isomer such as XLVI, since elemental analysis of this mixture agreed with that required for diethoxydihydropyran. Although the n.m.r. spectrum showed clear evidence for a mixture of two (possibly three) isomeric diethoxydihydropyrans, g.l.c. showed only a single, though broad, peak, hence their separation under the conditions employed (see Experimental) was not possible.

Hydrogenation of the above diethoxydihydropyran gave an oil which was shown by g.l.c. analysis to be a mixture of three substances, as indicated by three distinct peaks B, C and D (in order of appearance) in the area ration of 8:1:1. B was identical in retention time to that of authentic trans-2,3-diethoxytetrahydropyran, whose preparation is summarized in Chart 48.



(DME = 1,2-dimethoxyethane)

CHART 48

C and D are not due to cis-2,3-diethoxytetrahydropyran and are as yet unknown.

The n.m.r. spectrum of this mixture (whose elemental

analysis was correct for diethoxytetrahydropyran) showed a doublet at τ5.57 ($J_{2,3}$ = 4.0 Hz) for the anomeric proton. This along with other significant features (e.g. signals due to OC_2H_5) was identical to the spectrum of authentic trans-2,3-diethoxytetrahydropyran. However it did show the presence of a narrow multiplet at τ5.39 which could be the signal (or signals) for the anomeric proton (or protons) of an isomer (or isomers) such as 2,5-diethoxytetrahydropyran (hydrogenated XLVI) or 2,4-diethoxytetrahydropyran (hydrogenated XLVIII). The signal at τ5.39 was not due to cis-2,3-diethoxytetrahydropyran, another alternative structure, since this compound shows a doublet at τ5.18 ($J_{2,3}$=3 Hz) for H-2.

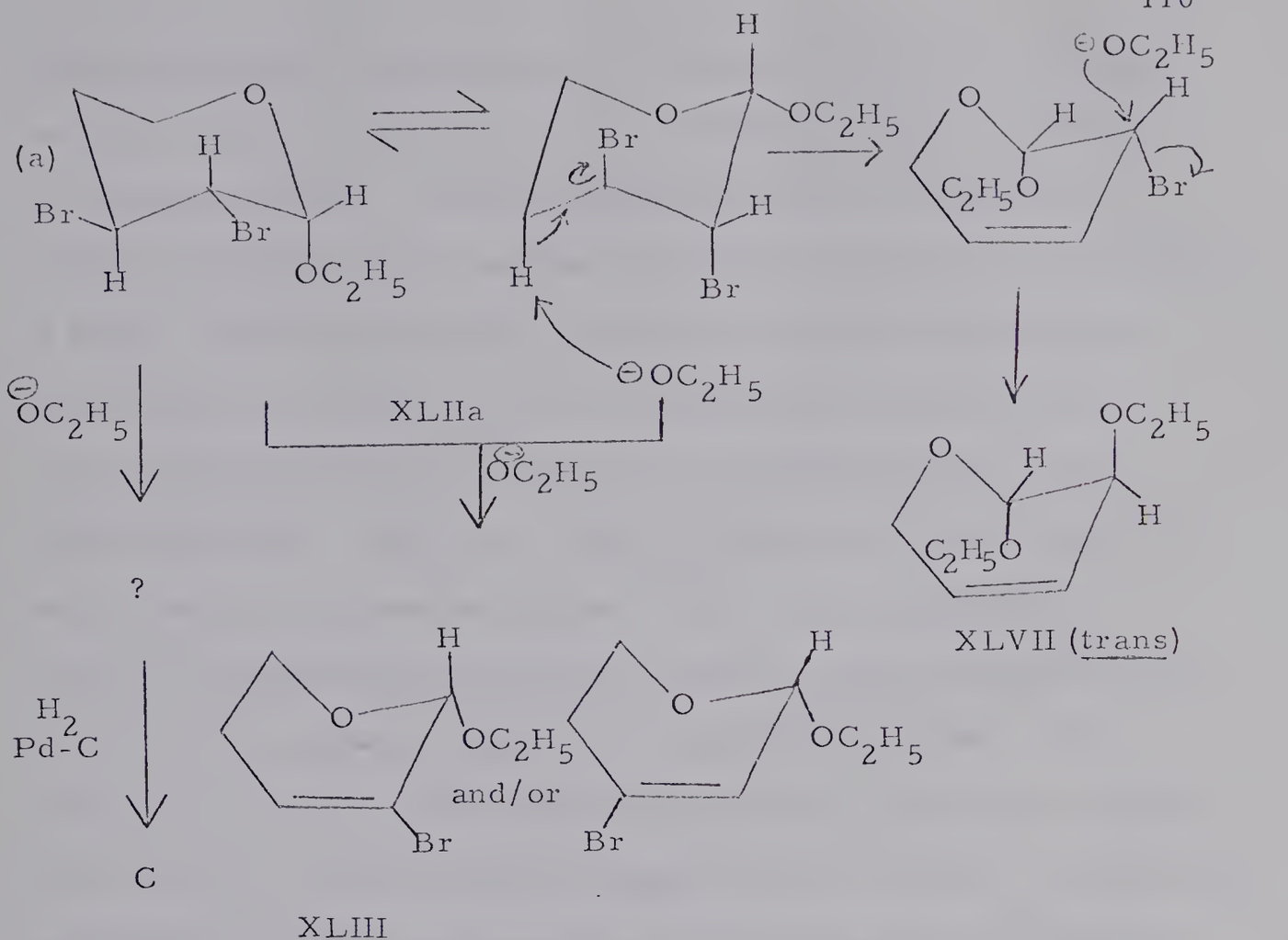
Additional information was obtained by g.l.c. analysis of the crude hydrogenated product obtained from dehydrobromination (with alcoholic base) of (i) the 3:1 mixture of XLIIa and XLIIb, (ii) the pure liquid isomer XLIIa, and (iii) the pure solid isomer XLIIb. In case (i), four distinct peaks were obtained A $\rightarrow$ D (in order of appearance) by g.l.c. in the area ratio of 12:8:1:1 respectively. The two major peaks A and B were identical in retention times with those of authentic 2-ethoxytetrahydropyran and trans-2,3-diethoxytetrahydropyran respectively. The origin of peaks C and D (isomers of B) is unknown. The 2-ethoxytetrahydropyran could have arisen from hydrogenation of both unchanged 3,4-dibromo-2-ethoxytetrahydropyran (XLIIa, XLIIb), and 3-bromo-2-ethoxy-5,6-dihydro-2H-pyran (XLIII) since both of these substances are known (75) to give 2-ethoxytetrahydropyran when catalytically hydrogenated. The actual proportion of peaks A to B depended upon the length of time of reaction of XLII

with the base. Trans-2,3-diethoxytetrahydropyran must have arisen from compound XLVII (Chart 41). The pattern B, C, D was identical with that obtained from the product of hydrogenation of the diethoxydihydropyran actually isolated from the 6:1 mixture obtained by treatment of XLII with base. This then, together with microanalytical data, indicates that C and D are very likely diethoxytetrahydropyrans.

Case (ii) involving liquid isomer XLIIa as starting material, gave three distinct peaks A, B and C (in order of appearance) in the area ratio of 13:9:1 and identical in pattern and retention times with A, B and C of case (i). Case (iii), involving the solid isomer (XLIIb) as starting material gave only two peaks A and D (in order of appearance) in the area ratio of 14:9, and identical in retention time with A and D of case (i).

It is thus clear that the 2,3-diethoxydihydropyran XLVII, which is the precursor of trans-2,3-diethoxytetrahydropyran, comes entirely from the liquid isomer XLIIa (which also produces unknown diethoxydihydropyran C), and that the solid isomer XLIIb produces an unknown diethoxydihydropyran D, (see Chart 49). It is also clear that the diethoxydihydropyran reported by Woods and Temin (75) is essentially trans-5,6-diethoxy-5,6-dihydro-2H-pyran XLVII and not XLIV.

The formation of trans-5,6-diethoxy-5,6-dihydro-2H-pyran (XLVII) from isomer XLIIa, deserves some comment. It has been observed, in the experience of this author, that the bromine atom in 3-bromo-2-ethoxytetrahydropyran is highly resistant to substitution. When heated with ethanolic sodium ethoxide (see Experimental) the only product obtained from this bromo compound was 2-ethoxy-5,6-


(a)
XLIIa
?
H2
Pd-C
C
and/or
XLIII
XLVII (trans)

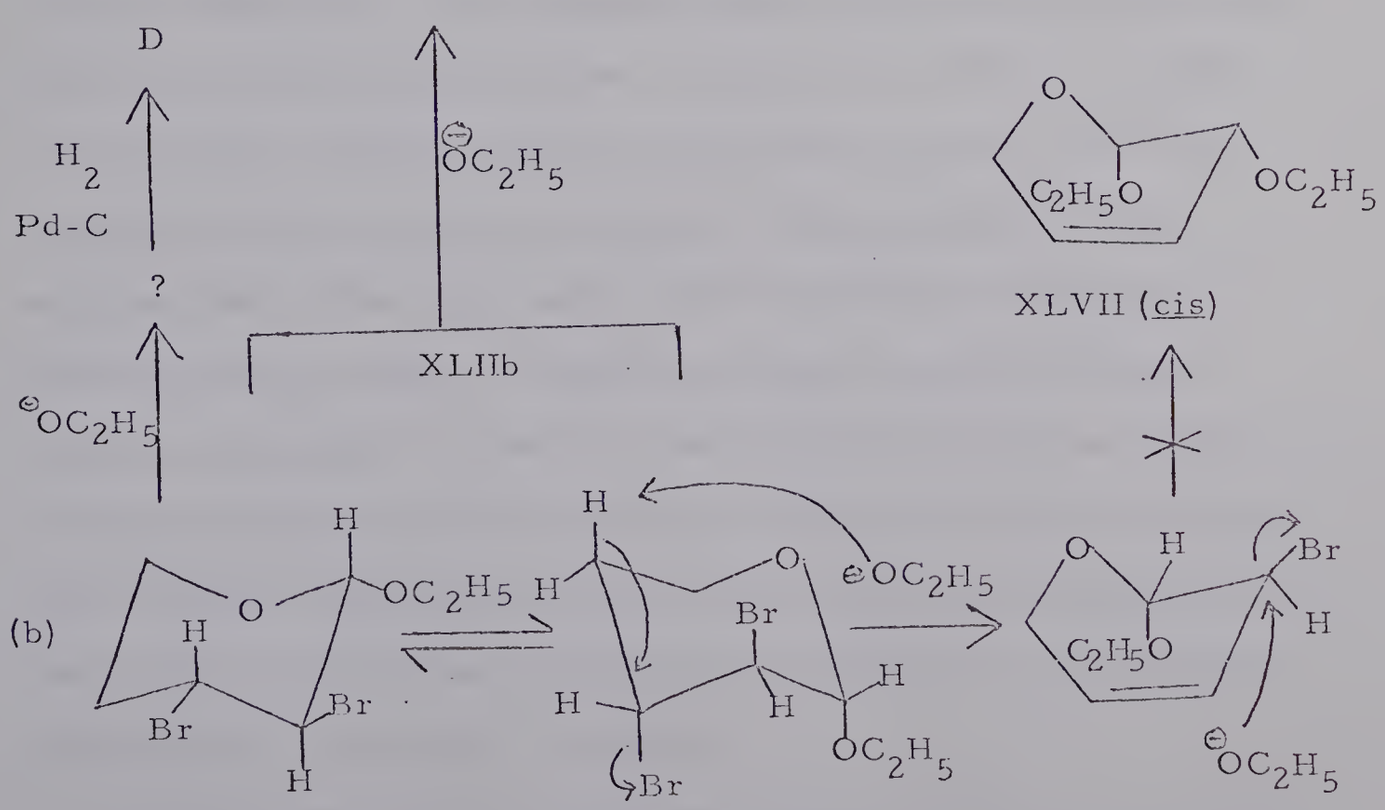
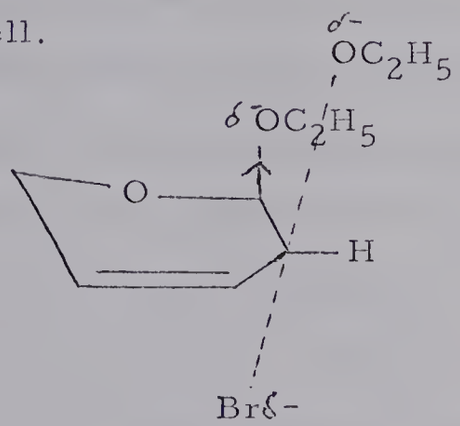

D
H2
Pd-C
?
XLIIb
XLVII (cis)
(b)

CHART 49

dihydro-2H-pyran, a consequence of dehydrobromination. In other attempts to effect substitution by use of ethanolic silver carbonate no reaction occurred. Hence substitution of the C-3 bromine in XLIIa by alcoholic base is unlikely as the first step towards formation of XLVII. It seems therefore reasonable to assume that dehydrobromination occurs first to give an allylic halide, followed by an S_N2 displacement by alkoxide ion of the now labile bromine atom ((a), Chart 49). The n.m.r. data for XLIIb and XLIIa (Charts 42 and 43, also see discussion of n.m.r. for these compounds in Section A) indicate that these isomers adopt a preferred conformation in which the two bromine atoms are equatorially oriented. It is well known, however, that dehydrohalogenation occurs more readily if the vicinal H and Br atoms are trans-diaxially oriented. Apparantly, both XLIIb and XLIIa can assume the conformation more amenable to dehydrohalogenation. The coupling between the anomeric proton and the proton on the adjacent carbon, in XLIIb, is 7.8 Hz in a solution of acetonitrile saturated with tetra-n-butylammonium bromide as compared with the coupling of 7.0 Hz in $CDCl_3$ solution. This indicates that, in the latter solvent there is present a significant amount of the conformer in which the bromine atoms are diaxial. This can reasonably be expected since a gauche interaction between the two bromine atoms has been relieved (36) and as well the anomeric effect (Chapter III) will add stability to this alternate conformation and thus counteract the strong 1,3-diaxial interaction of the C-4 bromine and the ethoxy group ((b), Chart 49).

If then both XLIIa and XLIIb are dehydrohalogenated, producing

respectively cis-5-bromo-6-ethoxy-5,6-dihydro-2H-pyran and trans-5-bromo-6-ethoxy-5,6-dihydro-2H-pyran, then attack by ethoxide ion on the cis isomer to produce trans-5,6-diethoxy-5,6-dihydro-2H-pyran via an S_N2 displacement of bromine appears to be easy. On the other hand, in an S_N2 displacement of bromine, approach by ethoxide ion, in the trans isomer would be hindered in the transition state by steric interference of the C-2 ethoxy group, and by polar repulsion as well.



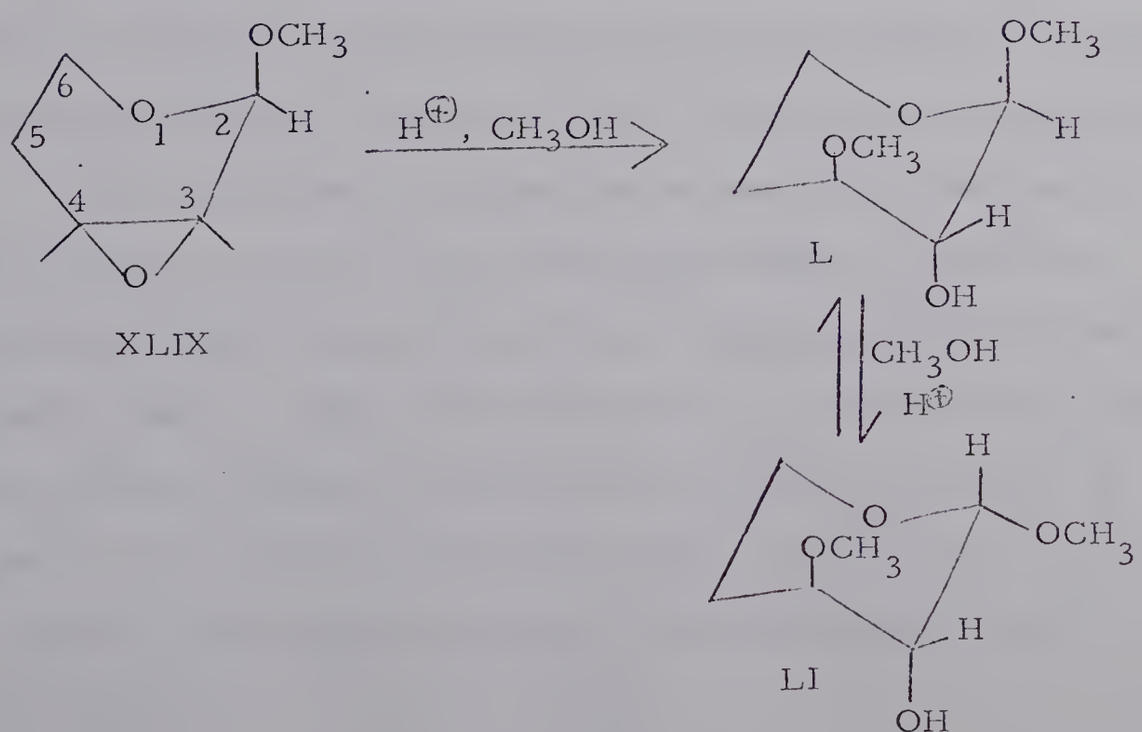
An alternate path of attack, e.g. via an S_Ni process, may then be favored. This possibility is supported by the fact that after hydrogenation, a diethoxydihydropyran (D, Chart 49) is obtained. This problem requires further investigation.

The foregoing discussion has shown that the reactions of Woods and Temin (75) yields some interesting information about pyran chemistry. However, because of the poor yields and complicated mixtures obtained up to the present time when 3,4-dibromo-2-ethoxy tetrahydropyrans are treated with alcoholic base, these reactions are not yet preparatively useful as a means of obtaining oxygen-substituted tetrahydropyrans.

VI. INTRODUCTION OF OXYGEN AT THE 2-, 3- AND 4-POSITIONS ON THE TETRAHYDROPYRAN RING.

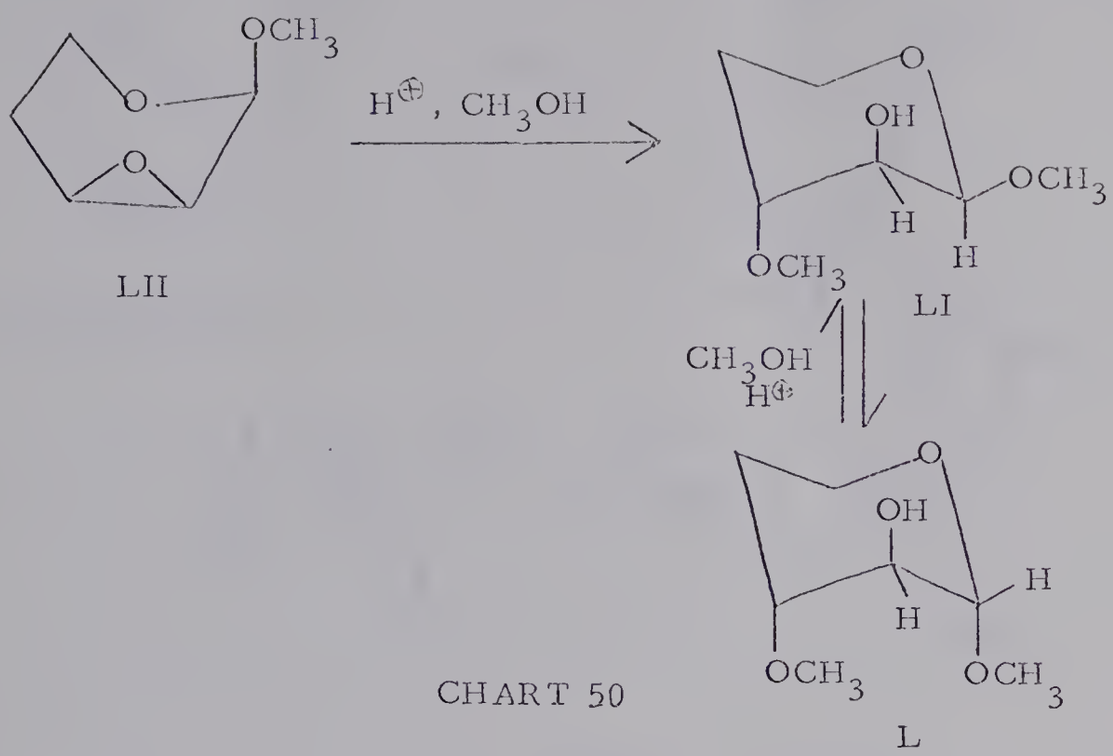
A. Preparation of methyl 4-deoxy-3-O-methyl-α,β-DL-threo-pentopyranoside.

In Chapter IV it was shown that both cis- and trans-2-alkoxy-3,4-epoxytetrahydropyran are attacked by lithium aluminum hydride exclusively at the epoxide carbon remote from the C-2 alkoxy substituent to give the corresponding cis- and trans-2-alkoxy-3-hydroxytetrahydropyrans (Chart 32, Chapter IV). The rationale which explained the reaction selectivity shown by these epoxides was next employed to prepare a mixture of methyl 4-deoxy-3-O-methyl -α- and β-DL-threo-pentopyranosides starting with the cis-, trans-, or cis,trans-3,4-epoxy-2-methoxytetrahydropyran (XLIX and LII, Chart 50).



XLIX

CHART 50



LII

LI

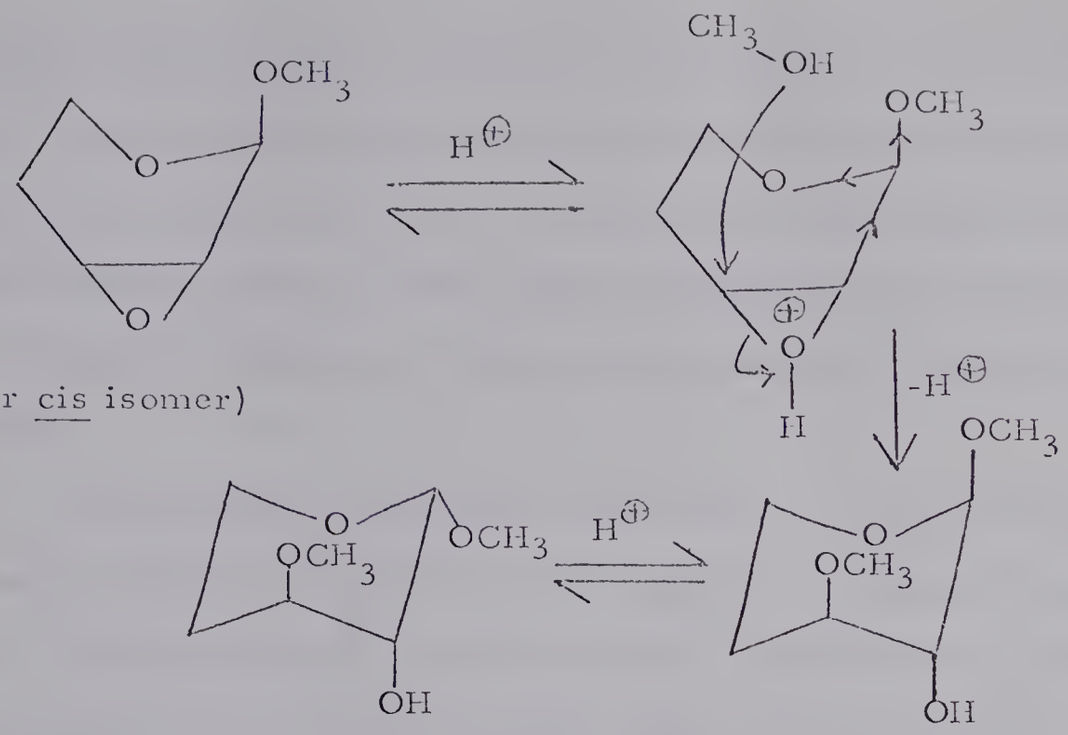
L

CHART 50

When XLIX and/or LII were heated in methanol containing a small amount of p-toluenesulfonic acid as catalyst, a distillable oil was obtained in76% yield, (Chart 50) which contained in each case the same mixture of just two substances as shown by g.l.c. and n.m.r. analysis. That these two substances were isomers was shown by elemental analysis of the binary mixture which was correct for methyl 4-deoxy-3-O-methyl-α (or β)-DL-threo-pentopyranoside.

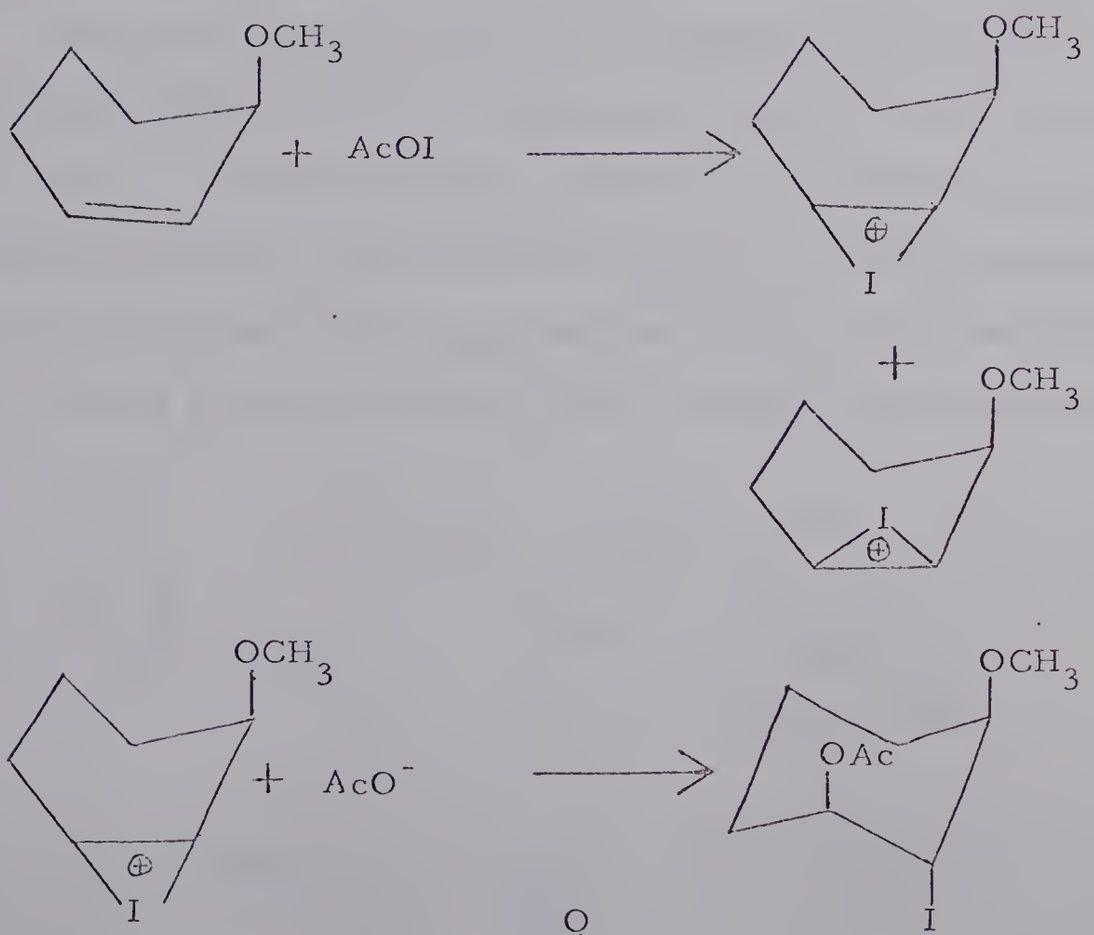
The results can be rationalized on the assumption that the first reaction to occur is that in which the methanol attacks the protonated epoxide exclusively on that carbon atom remote from the anomeric center. This is then followed by a slower isomerization of the product to produce an equilibrium mixture of the α and β anomers of the DL mixture ((a), Chart 51). Such exclusive opening of a cyclic "onium" species has been observed previously (64) ((b), Chart 51).

(a)



(or cis isomer)

(b) AgOAc I_2 AcOH AcO I AgI



(Ac = $CH_3-\overset{O}{\overset{\|}{C}}-$)

CHART 51

Kavadias (64) subjected 3-methoxycyclohexene to the Prevost reaction ((b), Chart 51) and found that in each of the two isomeric products obtained the iodine atom resided on the carbon atom adjacent to carbon atom bearing the OCH_3 group. Stereochemical and electronic (i.e. inductive) effects were deemed responsible for the observed results.

It is therefore reasonable to anticipate a similar behavior in the acid catalysed methanolysis of 3,4-epoxy-2-methoxytetrahydropyran, since in this case a substantial inductive effect is expected to be operational due to the C-2 dioxy portion of the molecule ((a), Chart 51).

The structure of the products L and LI (Chart 50) were proven in the following manner.

The isomeric mixture (L and LI) obtained from methanolysis of XLIX and LII (Chart 50) was hydrolysed under acid conditions and gave a syrup. Treatment of the syrup with phenylhydrazine gave a solid phenylosazone, which analyzed correctly for the phenylosazone of 4-deoxy-3-O-methyl-DL-threo-pentose, thus proving the location of the methoxy group at position 4 in the tetrahydropyran ring system.

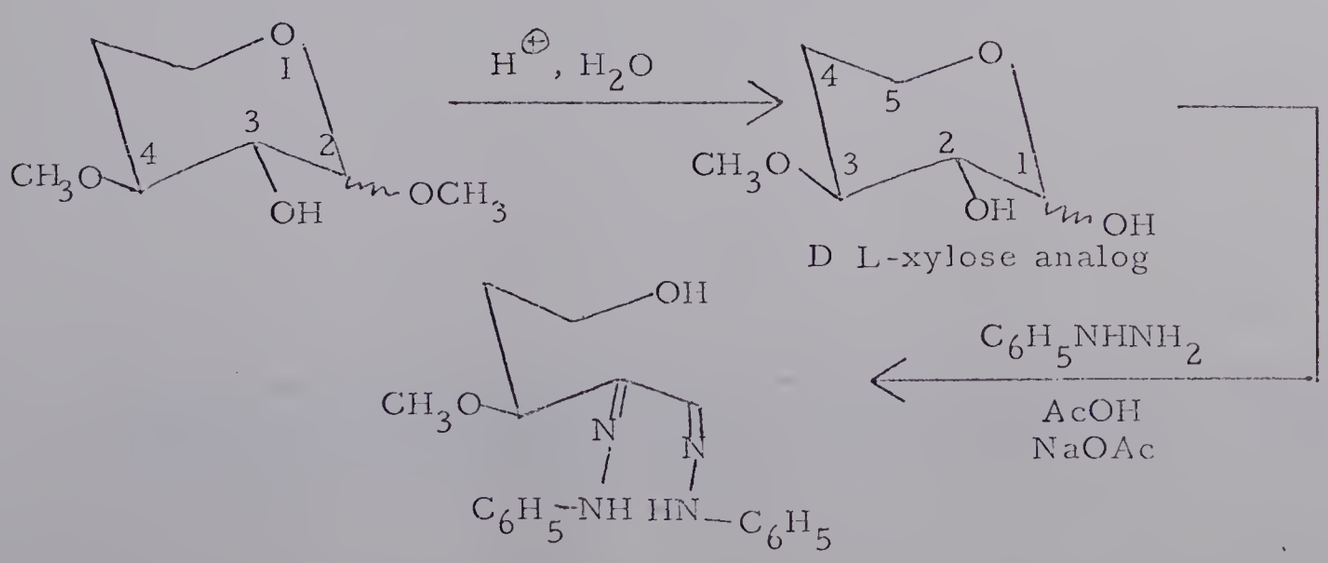
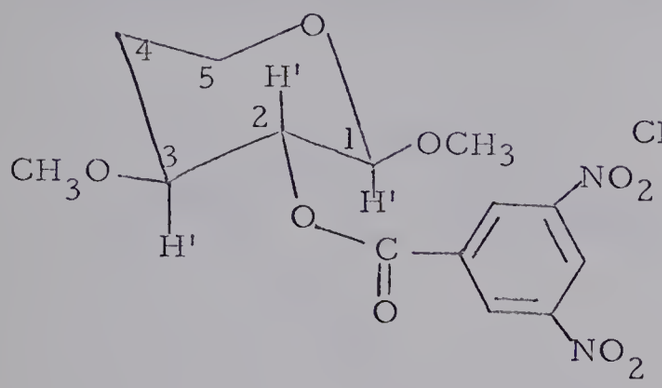
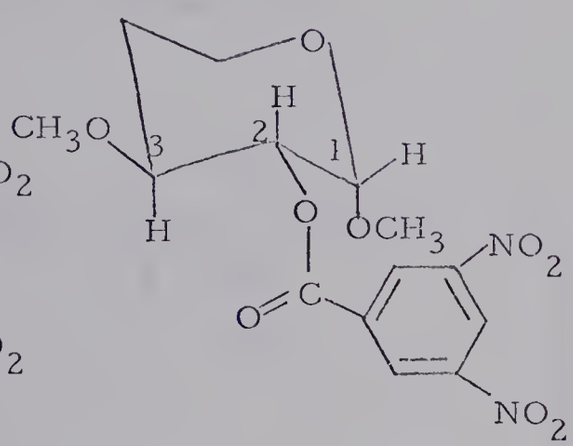


CHART 52

Conversion of the mixture L and LI (Chart 50) to the 3,5-dinitrobenzoate give a solid whose nuclear magnetic resonance spectrum showed doublets for the anomeric (H-1) protons at τ 5.55 ($J_{1',2'}$ = 7 Hz) and τ 5.03 ($J_{1,2}$ = 3.3 Hz) for the two epimers, and quartets centered at τ 4.92 ($J_{2',3}$ = 8 Hz and $J_{1',2'}$ = 3.3 Hz) for the protons H'-2 and H-2 on the carbon atom bearing the 3,5-dinitrobenzoyl group in the two anomers respectively*.





H'-1, τ 5.55 doublet

$J_{1',2'}$ = 7 Hz

H-1, τ 5.03 doublet

$J_{1,2}$ = 3.3 Hz

H'-2, τ 4.92 quartet

$J_{1',2'}$ = 7 Hz

$J_{2',3'}$ = 8 Hz

H-2, τ 4.97 quartet

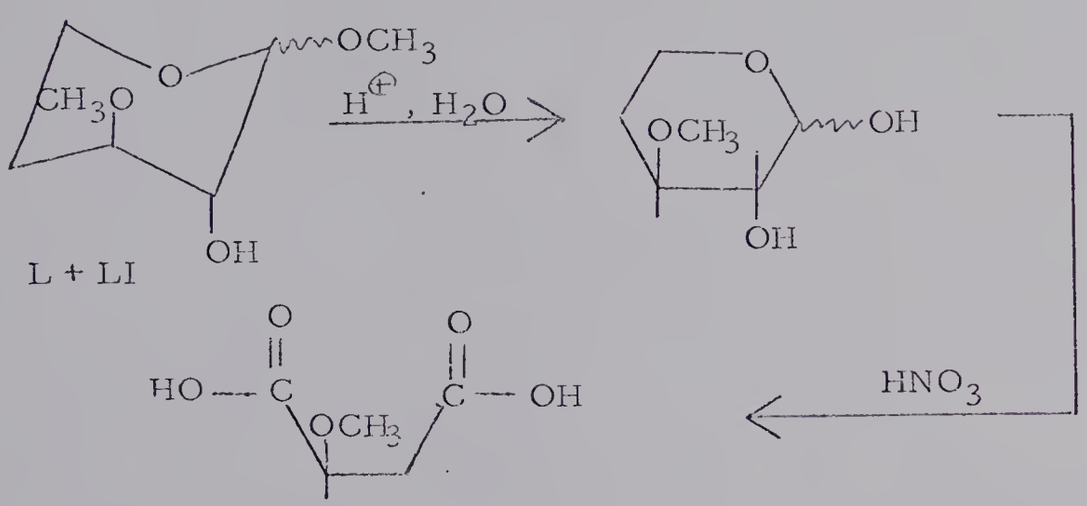
$J_{1,2}$ = 3.3 Hz

$J_{2,3}$ = 8 Hz

* Here the numbering is that for the xylopyranoside ring system in which the anomeric carbon is #1.

Irradiation of the signal position for the anomeric proton H' at τ 5.55 collapsed the quartet centered at τ 4.92 to a doublet centered at τ 4.92 ($J_{2',3}$ = 8 Hz) thus showing that the two protons concerned must be on adjacent carbon atoms and thus locating the position of the free hydroxyl group on carbon 2 of the xylopyranoside ring system.

The threo configuration was established on the basis of oxidative degradation, with concentrated nitric acid, of the syrup resulting from hydrolysis of L and LI (Chart 52).



O-methyl-DL-tartaric acid

There was obtained a solid, melting at 196°-202° (dec.). The infrared spectrum of this compound (Fig. 15) was practically identical with that of authentic O-methyl-L-tartaric acid (Fig. 16) which had been kindly donated by Dr. Woo et al* (90) who prepared it by nitric acid oxidation of 4,6-dideoxy-3-O-methyl-D-glucose (chalcose) and by methylation of authentic L-tartaric acid. The melting point of O-methyl-L-tartaric acid was 179°-182° (90) whereas

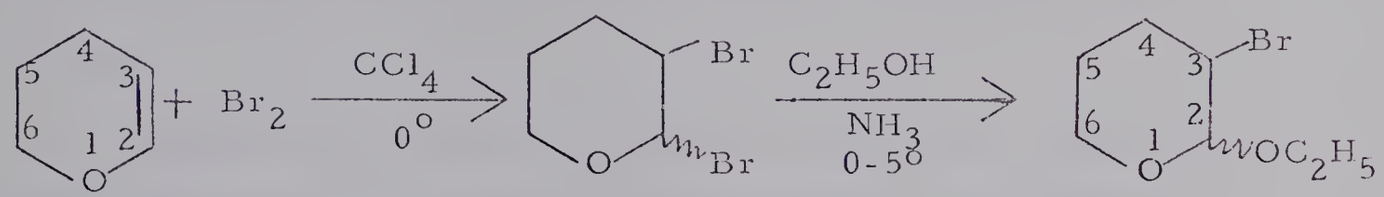
* The author is indebted to Dr. Woo and associates of Parke, Davis and Company, Detroit 32, Michigan, for their sample of O-methyl-L-tartaric acid and a copy of its infrared spectrum (Fig. 16).

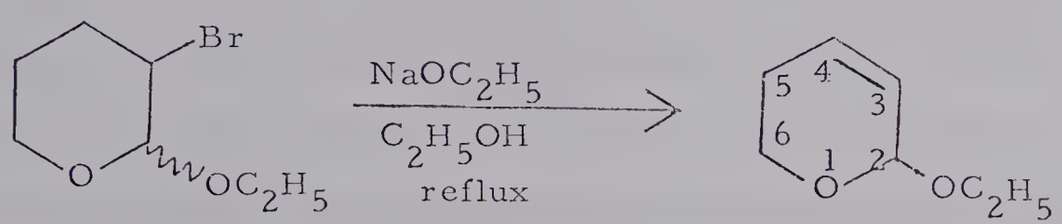
the DL-mixture melted at 196°-202°. This difference, however, is not surprising since it is known that DL-tartaric acid melts at a higher temperature than does the D or L isomer (91, 92).

VII. PREPARATION OF METHYL 4-DEOXY-6-O-METHYL-α-DL-ARABINO-HEXOPYRANOSIDE

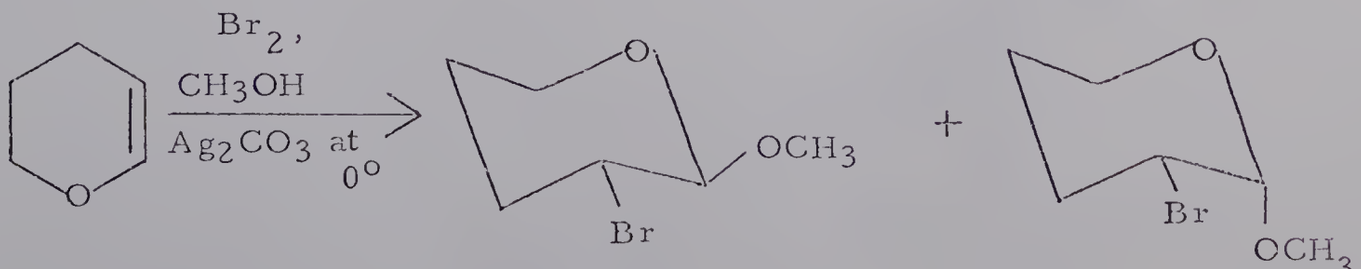
The 2-alkoxy-5,6-dihydro-2H-pyrans, used in this work and described in Chapters II, IV and V, were prepared in this laboratory according to a modification of known procedures (37, 56).

Woods and Sanders (56) prepared 2-ethoxy-5,6-dihydro-2H-pyran by the following sequence of reactions,





Lemieux and Fraser-Reid (37) prepared 3-bromo-2-methoxy-tetrahydropyran in the trans to cis ratio of 9:1, in one step from 3,4-dihydro-2H-pyran by addition of bromine to a mixture of the dihydropyran, methanol and silver carbonate at 0°.



trans : cis = 9 : 1

In the present work greater stereoselectivity was obtained, than in the previous case (37), when bromine was added to a solution of 3,4-dihydro-2H-pyran and liquid ammonia in methanol at -60°. The trans to cis ratio of the bromo compound thus obtained was found to be 99:1 by g.l.c. and by Lemieux and Fraser-Reids's method of analysis using n.m.r. (37). This highly selective method for obtaining trans-2-alkoxy-3-bromotetrahydropyrans was used throughout the present study. The bromides obtained were dehydrobrominated to give the corresponding 2-alkoxy-5,6-dihydro-2H-pyrans.

Addition of bromine to a solution of 2-methoxymethyl-3,4-dihydro-2H-pyran in a mixture of liquid ammonia and methanol at -60°, gave an oily distillable product in 87% yield (Chart 53). Because the analogous compound 3,4-dihydro-2H-pyran had given essentially (99%) trans-3-bromo-2-methoxytetrahydropyran under the same conditions of reaction, LIII and LIV (Chart 53) were assigned as the structures of the compounds obtained from the present reaction. Elemental analysis also supported these structures.

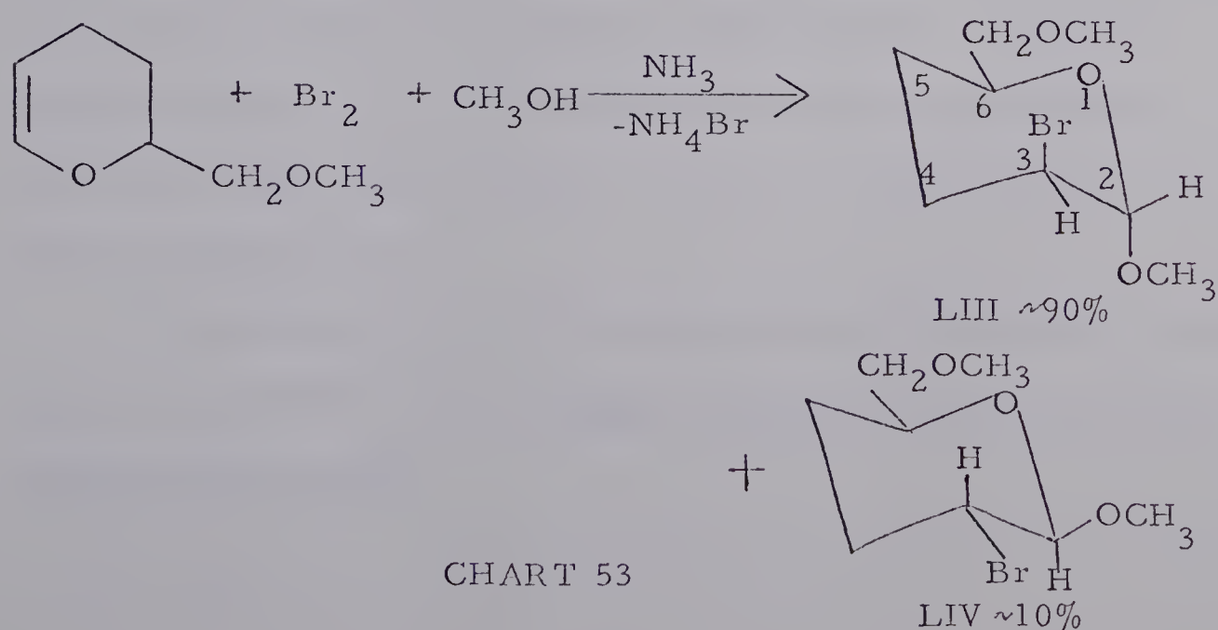
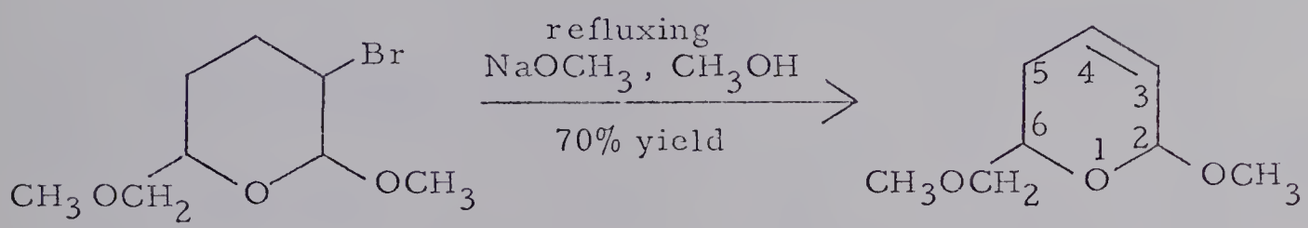


CHART 53

The n.m.r. spectrum (Fig. 17) of the product similarly supports structures LIII and LIV. The spectrum of the mixture in $CDCl_3$ solution shows two signals in the anomeric (H-2) region at τ 5.28 (symmetrical envelope, $\frac{w}{2} \sim 3$Hz) and τ5.71 (doublet of spacing 9.2 Hz) in the area ratio of 9:1 respectively. The higher field doublet was assigned to structure LIV and the lower field envelope (representing the major component in the isomeric mixture) was assigned to LIII for reasons already discussed in Chapter I, Section A.

Treatment of the 9:1 isomeric mixture of LIII and LIV with sodium methoxide in boiling methanol gave a 70% yield of an olefin, shown by g.l.c. to contain apparently one component. These

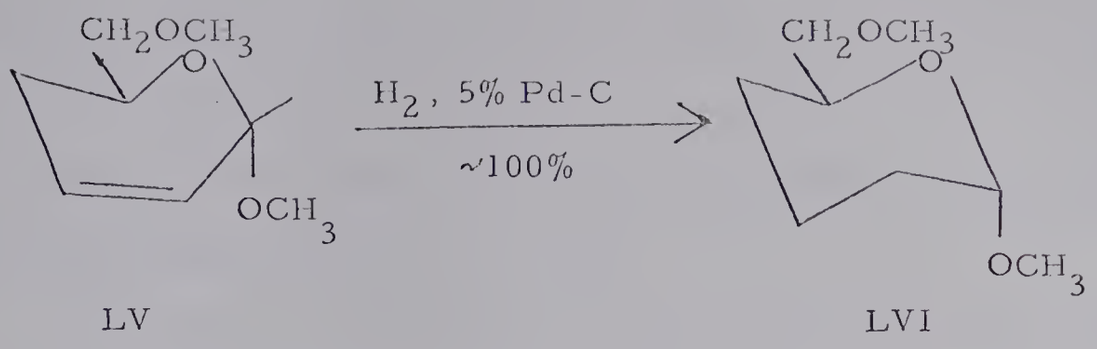


(LIII + LIV) LV

CHART 54

conditions are known (56) to produce only 2-alkoxy-5,6-dihydro-2H-pyrans from 2-alkoxy-3-bromotetrahydropyrans. Elemental analysis and the n.m.r. spectrum of the olefin agreed with the structure as cis- and/or trans-2-methoxy-6-methoxymethyl-5,6-dihydro-2H-pyran (LV).

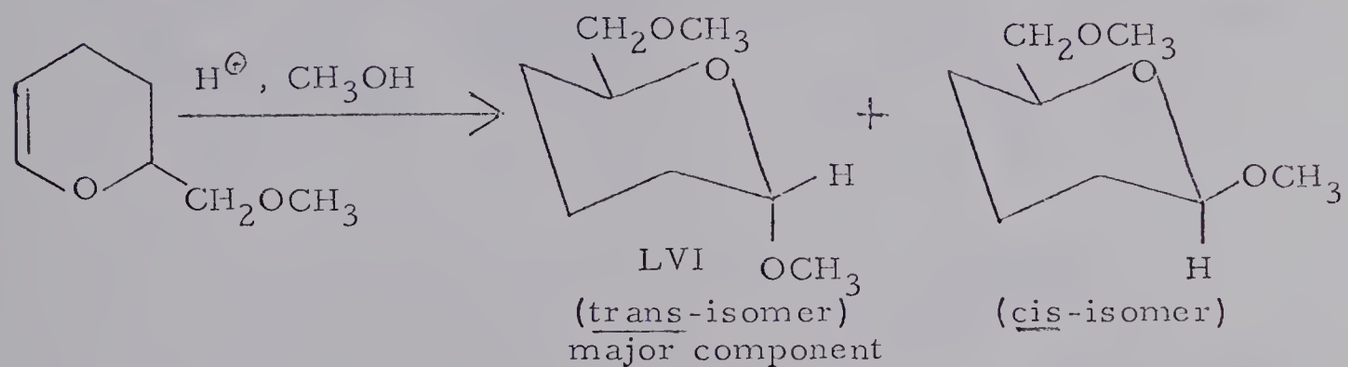
The olefin (LV) was hydrogenated over 5% palladium-carbon to give a quantitative yield of trans-2-methoxy-6-methoxymethyl-tetrahydropyran (LVI).



LV LVI

CHART 55

The identity of LVI as trans-2-methoxy-6-methoxymethyltetrahydropyran was established by the n.m.r. spectra and g.l.c., which were identical to those of an authentic sample, which had been prepared (93) according to the following reaction



LVI (trans-isomer) major component

(cis-isomer)

The cis and trans isomers* of 2-methoxy-6-methoxymethyltetrahydropyran had also been separated by preparative g.l.c. (93) and found to possess distinctly different physical and spectroscopic (g.l.c. and n.m.r.) characteristics.

On the basis of the above information it can be concluded that LV (Chart 54) was trans-2-methoxy-6-methoxymethyl-5,6-dihydro-2H-pyran (LVI). Accordingly, the 3-bromo precursor of LV must

* Authentic samples of cis- and trans-2-methoxy-6-methoxymethyltetrahydropyran were prepared in this laboratory by U. E. Diner (93), and thus were available for comparison.

have been LIII (Chart 53). The fact that the olefinic product (LV) obtained by dehydrohalogenation of the mixture of bromides LIII and LIV (Chart 53) showed one peak by g.l.c. analysis, and hydrogenation of the olefin produced only LVI indicates that apparently one isomer only (LIII) dehydrohalogenates readily.

Treatment of LV with m-chloroperoxybenzoic acid in ether solution at ~35° for 7 days gave an 80% yield of a distillable oil containing two components (g.l.c. and n.m.r. analysis) in the approximate ratio of >95: <5.

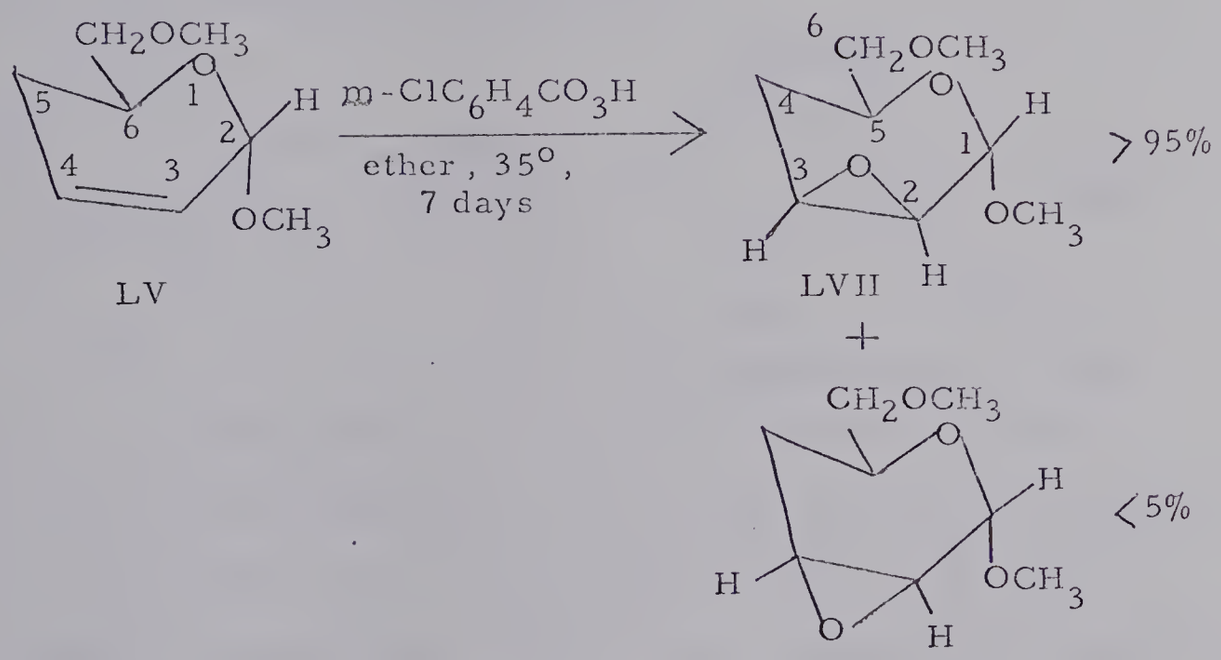


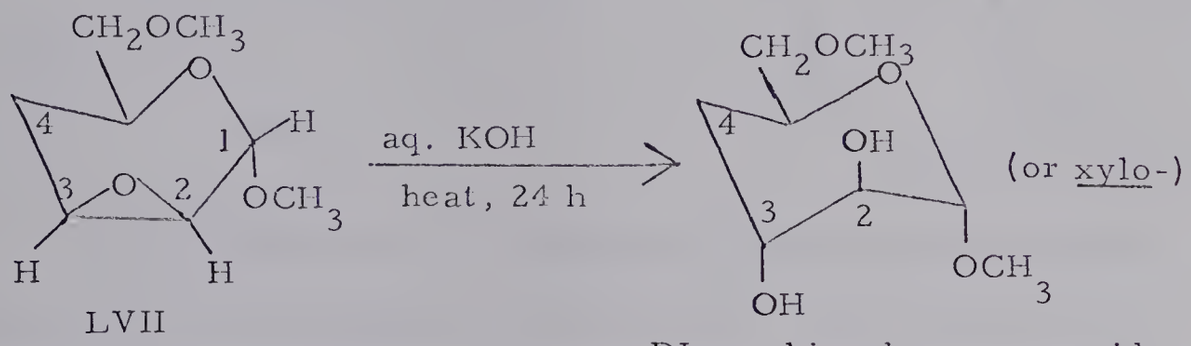
CHART 56

Elemental analysis of the product was correct for methyl 2,3-anhydro-4-deoxy-6-O-methyl-α-DL-lyxo-hexopyranoside (LVII). The n.m.r. spectrum of LVII* (Fig. 11) shows a sharp singlet due to H-1 at τ5.18 and a doublet at τ7.10 with a spacing of 4.0 Hz. It was shown in

* LVII, Chart 56 and XXXIX, Chart 39 in Chapter IV represent the same compound.

Chapter IV, section C, that the occurrence of these two signals is characteristic of a trans relationship between the anomeric (C-1) methoxy group and the 2,3-epoxy function in tetrahydropyrans and in pyranosides. Since it was also established (Chart 55) that the 6-methoxymethyl group and 2-methoxy group are trans to each other in LV, the correct structure of LVII must be that represented in Chart 56.

Treatment of LVII (contaminated with <5% of the isomeric epoxide) with hot aqueous potassium hydroxide gave a syrup which resisted many attempts at crystallization.



LVII

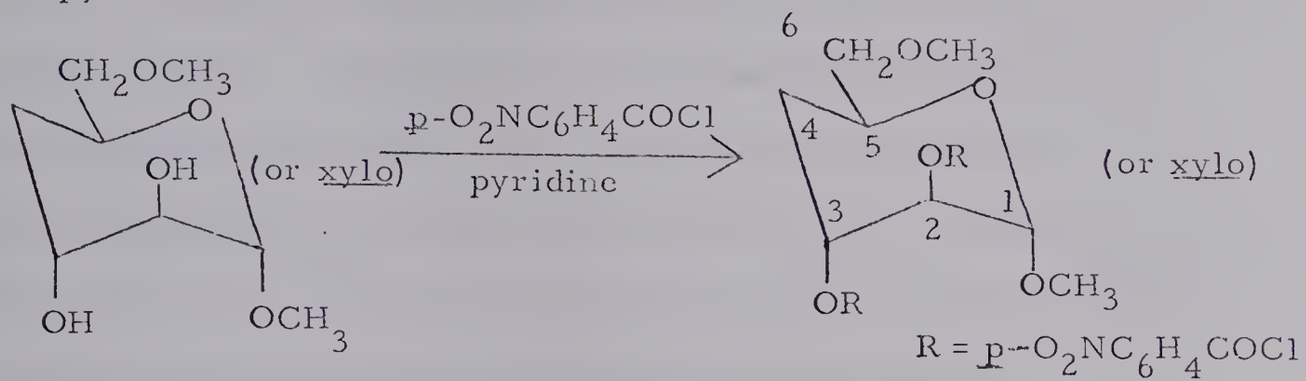
DL-arabino-hexopyranoside

In the above reaction both stereochemical and electronic effects (see Chapter IV) are expected to favor epoxide ring opening predominantly or exclusively at C-3, to give methyl 4-deoxy-6-O-methyl-α-DL-arabino-hexopyranoside. The exclusive opening of a 2,3-epoxide at C-3 in a 4-deoxyhexopyranoside to give the corresponding trans-diaxial diol has been previously reported (96) and is discussed in detail in Chapter VIII.

The 60 MHz n.m.r. spectrum of the syrupy product in $CDCl_3$ showed one broad singlet in the anomeric (H-1) region at τ5.36 which would support either the arabino or xylo configuration of the product of hydrolysis of LVII. As well, integration of the spectrum gave a

proton count correct for the arabino or isomeric xylo hexopyranoside. From these two facts, no decision could be made concerning the stereochemistry about C-2 and C-3 of the syrupy hydrolysis product.

Reaction of the syrup with excess p-nitrobenzoyl chloride in pyridine gave a solid derivative which melted sharply at 131-132°. The elemental analysis of the solid was correct for the di-p-nitrobenzoate of methyl 4-deoxy-6-O-methyl-α-DL-arabino (or xylo-)-hexopyranoside.



The 100 MHz n.m.r. spectrum of the di-p-nitrobenzoate (Fig. 23) in $CDCl_3$ showed a broad "singlet" (one proton) in the anomeric region at τ 5.11. Two multiplets each integrating for one proton were observed below the anomeric region at τ4.60 and τ4.85. These signals are undoubtedly due to the protons on C-3 and C-2 which are shifted downfield because of the deshielding effect of the p-nitrobenzoyloxy groups at these carbons. Since no other signals are observed in or near the anomeric region apparently the p-dinitrobenzoate is isomerically pure. Spin decoupling was carried out on this compound. The results of this experiment supports the arabino configurational assignment for the hexopyranoside obtained from LVII.

The obvious assignment is that of the "singlet" at τ 5.11 for

the anomeric proton H-1. The triplet of doublets and the multiplet at high field centered at τ 7.80 and τ 8.20 respectively can be assigned reasonably to the two protons on C-4. The two low field multiplets at τ 4.60 and τ 4.85 are undoubtedly due to C-3 and C-2. Their exact assignment will be made later from decoupling results. The signals due to the C-1 and C-6 OCH_3 groups appear as singlets at τ 6.53 and τ 6.60. Since H-5 is coupled to at least 4 protons (H-4a, H-4e and the two C-6 protons) it is expected to have a complex splitting pattern. Therefore the broad multiplet which integrates for one proton centered at τ 5.61 is most likely due to H-5. The remaining doublet centered at τ 6.47 (J=4.5 Hz) is reasonably assigned to the two C-6 protons since they are coupled to one proton (H-5) and are expected to absorb in this region of the spectrum.

Irradiation of the broad multiplet at τ 5.61, tentatively assigned to H-5, caused the doublet at τ 6.47 (J=5 Hz) to collapse to a singlet and the high field triplet of doublets at τ 7.80 to collapse to a broad doublet with a spacing of 14 Hz. Also the signals at τ 4.60 and τ 4.85 became sharper indicating long range coupling between H-5 and H-3, H-2. This information clearly shows that the H-5 signal is the multiplet at τ 5.61 since strong coupling is expected between the axial H-5* and the axial C-4 proton, to which the signal

* In Chapter III it was shown that in 2,3-disubstituted 6-methoxymethyltetrahydropyrans the 6-methoxymethyl group is equatorial. Therefore the C-6 hydrogen (H-5 in pyranosides) is in the axial position. In the present analogous case, then, it can be assumed that H-5 is in the axial position. This assumption is borne out by the large coupling which is removed when H-5 is irradiated.

at τ7.80 is now assigned. Furthermore the assignment of the doublet at τ6.48 to H-6 is confirmed.

Irradiation at H-1 at τ5.11 resulted in a sharpening of the signal at τ4.60, however, the multiplet at τ4.85 was obscured by a beat frequency signal.

Irradiation of the multiplet at τ4.60 caused the signal centered at τ7.80 (H-4a) to collapse to a quartet with spacings of 14 Hz and 10.5 Hz. Also there was a slight but observable change in the pattern of the multiplet centered at τ8.20 (H-4e). The low field multiplet must therefore be due to H-3, and the H-3, H-4a coupling constant is $J_{3,4a}$ = 3.5 Hz. From the H-4a quartet obtained when H-3 is irradiated and the broad doublet of 14 Hz obtained when H-5 is irradiated it is clear that $J_{4a,5}$=10.5 Hz and $J_{4a,4e}$ = 14 Hz. The small coupling between H-3 and H-4a ($J_{3,4a}$=3.5 Hz) indicates the C-3 proton to be in the equatorial position. Also the value $J_{4a,5}$=10.5 Hz confirms the trans-diaxial arrangement for H-5 and H-4a. (See Chapter I for a discussion of the coupling constant as a function of the dihedral angle of vicinal protons.)

Irradiation of H-4a (τ7.80) caused the signal due to H-3 at τ4.60 to decrease in width, from $\frac{w}{2}$ = 8 Hz to $\frac{w}{2}$ = 5 Hz. The remaining low field multiplet at τ4.85 which can now be assigned to H-2 formed a sharp quartet with couplings of 1.5 Hz and 3.5 Hz. These couplings must be $J_{1,2}$ and $J_{2,3}$. Unfortunately their specific assignments cannot be made on the basis of decoupling experiments since the signals for H-1 and H-2 are too close to permit observation of one of them while the other proton is being irradiated. However,

H-1 is equatorial* and H-3 was shown to be equatorial by virtue of its small coupling to H-4a ($J_{3,4a}$ = 3.5 Hz). Therefore, since $J_{2,3}$ is either 1.5 Hz or 3.5 Hz, H-2 must be equatorial and also trans to both H-1 and H-3.

The above information supports the configurational assignment for the syrupy compound obtained from alkaline hydrolysis of LVII as being that of methyl 4-deoxy-6-O-methyl-α-DL-arabino-hexopyranoside.

The stereoselectivity in the sequence of reactions leading to LVII is interesting. In Chapter IV, Section B, it was shown that the C-2 substituent of 2-methoxymethyl-3,4-dihydro-2H-pyran exerts a stereochemical influence on the direction of epoxidation of the double bond with the result that epoxidation occurs on the side of the ring opposite to the C-2 methoxymethyl group. Bromo-methoxylation of the same compound, however, appears to be influenced in exactly the opposite manner. Introduction of bromine occurs predominantly on the same side of the pyran ring as that occupied by the C-2 methoxymethyl substituent (Chart 53). Obviously, steric hindrance does not play a significant role in the latter reaction.

It was previously suggested in Chapter V that bromination of

* In Chapter IV it was shown that the C-1 methoxy group in LVII has the α configuration. Anomerization or hydrolysis does not occur at C-1 in pyranosides under alkaline conditions (96). Therefore, base catalysed hydrolysis of the 2,3-epoxy group in LVII is expected to give a product in which the C-1 OCH_3 group retains the α configuration. This being the case, H-1 in the hexopyranoside derived from LVII must possess the β configuration and is therefore equatorial.

2-ethoxy-5,6-dihydro-2H-pyran might involve complexation of bromine with the 2-ethoxy oxygen prior to formation of a cyclic bromonium ion (see Chart 44, page 101). Application of this view to the present case permits rationalization of the observed results. This is shown in Chart 57.

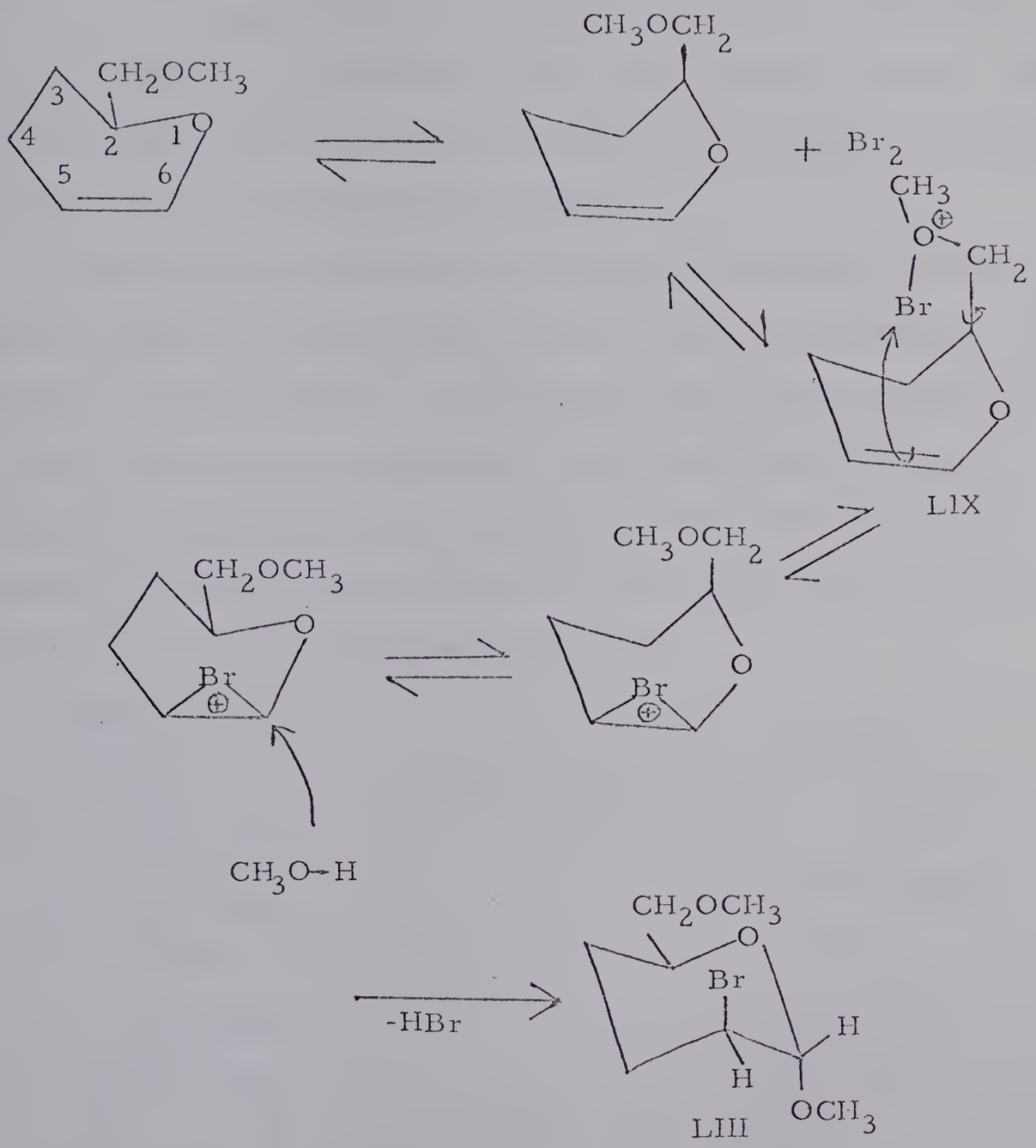


CHART 57

Examination of models shows that when the bromine-oxygen complex,

represented as LIX in Chart 57, is in the conformation in which the C-2 CH_2OCH_3 is in the quasi-axial position, the complexed bromine atom is placed directly above the π orbital of the double bond. In such a geometrically ideal situation, intramolecular transfer of the bromonium ion is expected to be easy. Under the reaction conditions, the 5,6-cyclic bromonium ion is opened by methanol resulting in a trans arrangement of the bromine atom and the methoxy group. (See the discussion of the bromo-methoxylation of the analogous 3,4-dihydro-2H-pyran, at the beginning of this chapter).

The essentially exclusive formation of the olefin, LV (trans), from the major component (LIII)of the 9:1 mixture of bromides, LIII and LIV, is understandable. In LIII the C-3 Br is axial whereas in LIV the bromine atom is equatorial. It is well known (94) that base catalysed dehydrohalogenation occurs much more rapidly when the hydrogen and halogen atoms involved are in a trans-diaxial, rather than à diequatorial, arrangement (Chart 58).

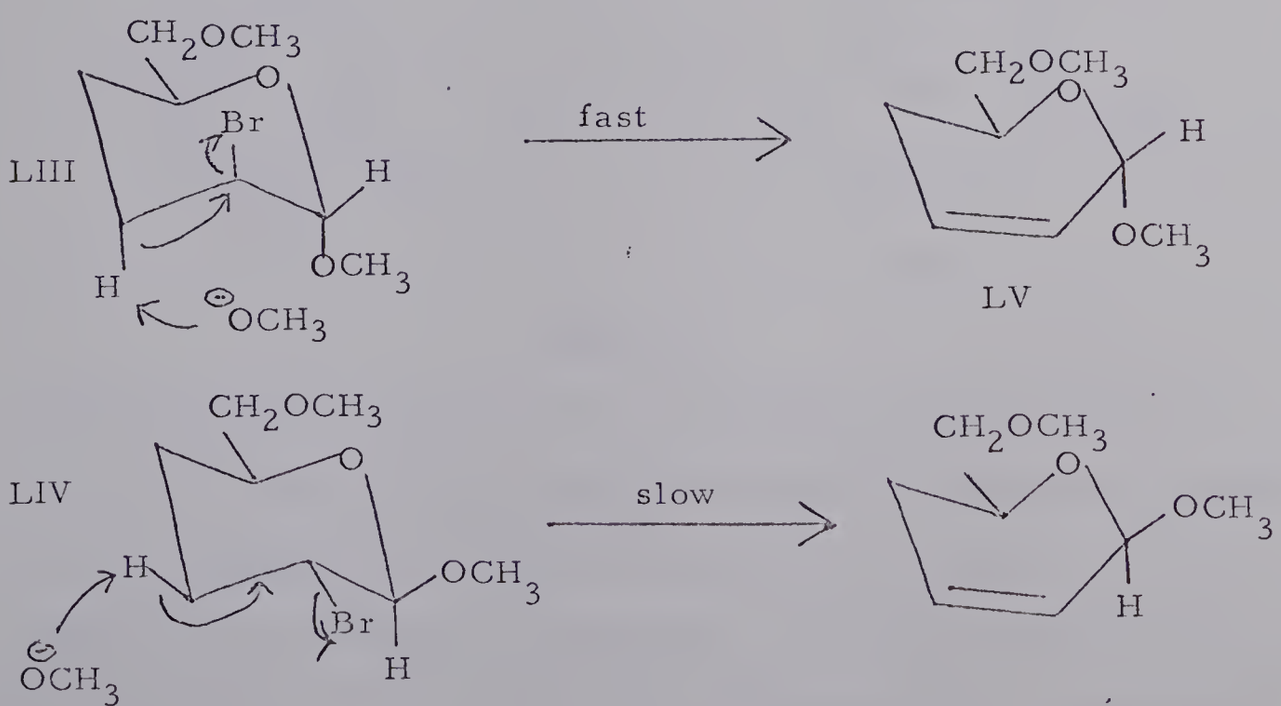
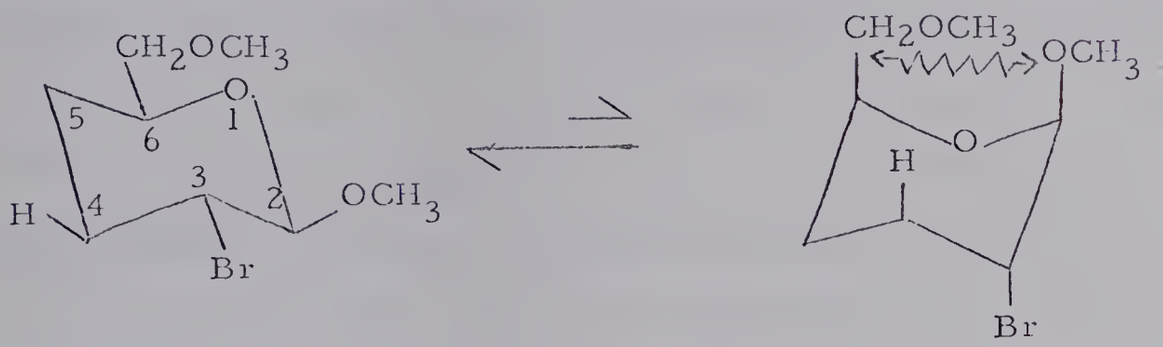


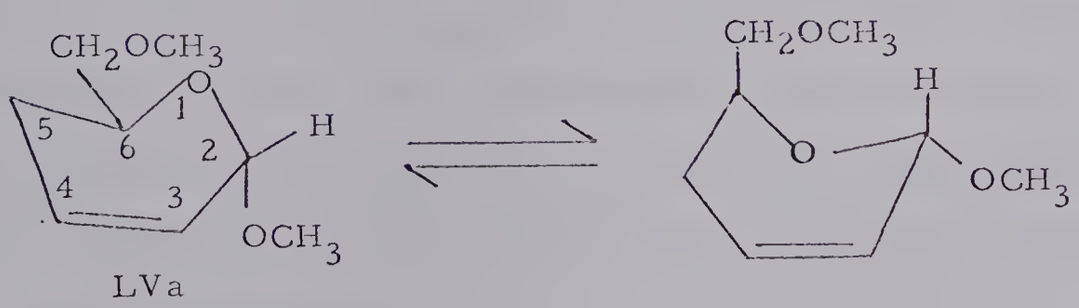
CHART 58

The isomer LIII is most likely in the preferred conformation (Chart 58) in which trans-diaxial dehydrohalogenation can readily occur. However LIV would have to assume the sterically unfavorable all-axial conformation in order for a similar elimination reaction to occur.



It is therefore clear that LIII should be much more amenable to dehydrohalogenation than is the isomer LIV, and satisfactorily explains the practically exclusive formation of the trans isomer LV.

The preferential epoxidation of LV to LVII poses perhaps the most interesting questions. The structure LV can be written in two alternative semi-chair forms,



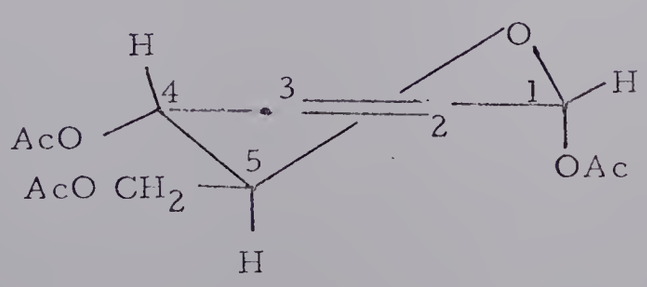
LVa LVb

CHART 59

Conformer LVa is expected to be more stable than LVb since the former possesses not only a quasi-equatorial C-6 CH_2-OCH_3 group, but also a quasi-axial C-2 OCH_3 group which is stabilized by the anomeric effect (Chapter II, section B). This by no means rules out the existence of LVb since in the dihydropyran ring system axial

and equatorial positions are not as distinctly different as they are in the tetrahydropyranyl analog. Based on stereochemical arguments developed in Chapter III, Section B, for conformer LVb epoxidation would be expected to take place mostly trans to the C-6 substituent. However, observations of the epoxidation of analogous compounds, described in Chapter IV, would predict that conformer LVa should lead to a 3,4-epoxide trans with respect to the C-2 OCH_3 group. Experimentally, the latter is found to be the case. If LVa and LVb are present to the same extent in the equilibrium the results indicate that the C-2 OCH_3 group is more effective than is the C-6 CH_2OCH_3 group in sterically hindering epoxidation. If, on the other hand, it is assumed that both groups are equally effective in preventing epoxidation to the same side of the ring on which they are located, it would be concluded that conformer LVa predominates.

Recently, Ferrier and Sankey (95) presented n.m.r. evidence for several acetylated hexenopyranosides each containing a double bond between C-2 and C-3 (C-3 and C-4 in the pyran numbering) which indicated that the CH_2OAc group prefers the quasi-equatorial position, especially when the substituent at C-1 is quasi-axial and trans to the C-5 substituent.

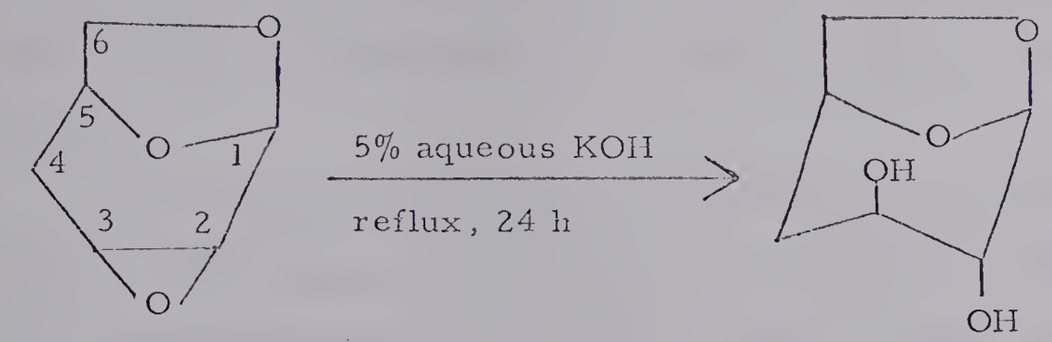


Ac = $CH_3-\overset{O}{\overset{\|}{C}}-$

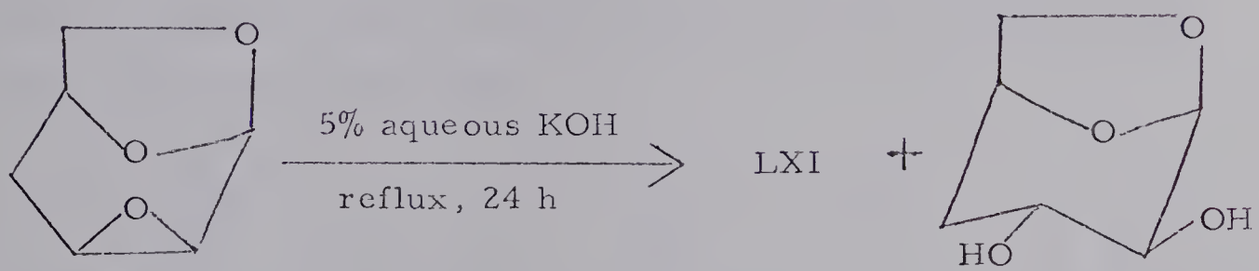
Based on these findings of Ferrier and Sankey, the conclusion can be tentatively drawn that conformer LVa, in which the C-6 CH_2OCH_3 group is equatorial, is preferred to LVb (Chart 59). In this preferred conformation, then, the quasi-axial C-2 OCH_3 group (Chart 59) is responsible for the selective formation of methyl 2,3-anhydro-4-deoxy-6-O-methyl-α-DL-lyxo-hexopyranoside.

VIII. PREPARATION OF 1,6-ANHYDRO-4-DEOXY-β-DL-XYLO-HEXOPYRANOSE

In 1961 Černý et al (96, b) obtained 1,6-anhydro-4-deoxy-β-D-xylo-hexopyranose (LXI) by treating 1,6:2,3-dianhydro-4-deoxy-β-D-ribo-hexopyranose (LX) with hot aqueous potassium hydroxide (Chart 60).



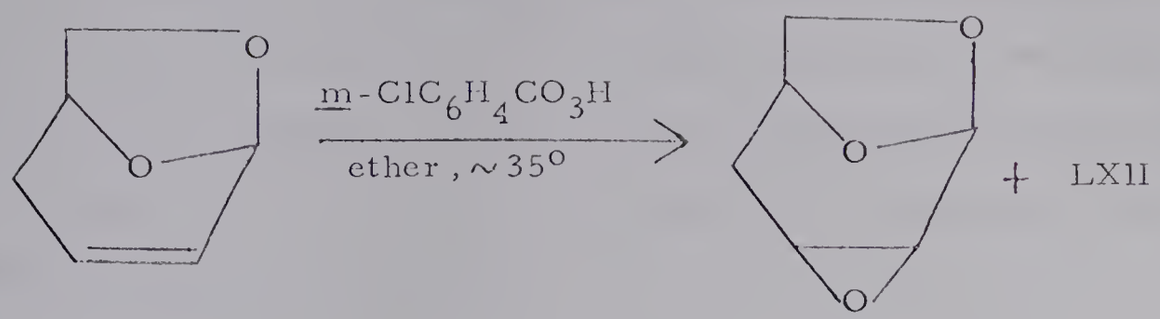
LX LXI



LXII CHART 60 LXIII

However, when these workers subjected 1,6:2,3-dianhydro-4-deoxy-β-D-lyxo-hexopyranose (LXII) to the same conditions a mixture was obtained consisting of LXI and 1,6-anhydro-4-deoxy-β-D-arabino-hexopyranose (LXIII, Chart 60) (96, a and b).

Structure LX can be viewed as an epoxy pyran. Using as a basis the work described in Chapters IV and VII, in this thesis, this "trans epoxide" should be obtainable by epoxidation of the appropriate dihydropyran (LXIV, Chart 61).

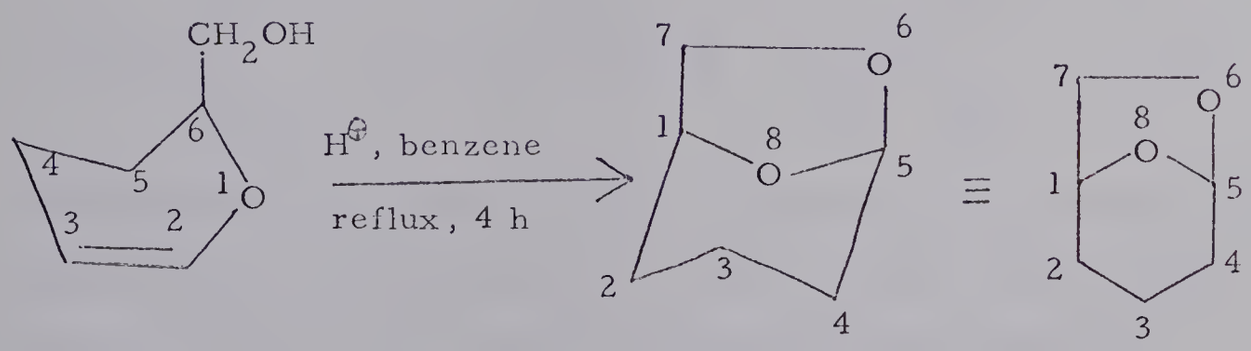


LXIV LX

CHART 61

Treatment of the DL-olefin LXIV with m-chloroperoxybenzoic acid is expected to give predominantly a DL-mixture of LX, as shown in Chart 61.

A search of the literature revealed that LXIV had not yet been prepared, although the saturated analog, 6,8-dioxabicyclo[3·2·1]-octane (LXVI), has been reported and is readily prepared (97, 98) from the "acrolein dimer alcohol", LXV, by acid-catalysed cyclization of the latter (Chart 62).

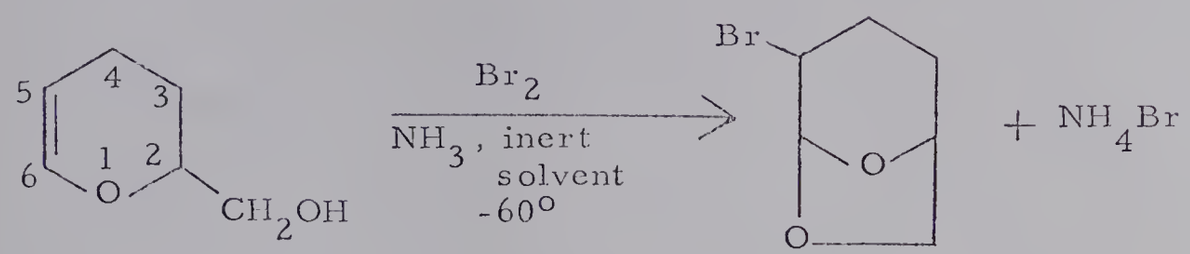


LXV LXVI

CHART 62

Dehydrohalogenation of the 4-bromo derivative of LXVI would be expected to give the olefin LXIV. The conversion of this olefin (LXIV) to the epoxy carbohydrate, LX, with subsequent epoxide opening to give compound LXI should then be possible. The key to this synthesis was the preparation of the C-4 bromide of LXVI.

A somewhat modified route based upon the bromomethoxylation (with bromine and methanol) of 3,4-dihydro-2H-pyrans (see Chapter VII) was first attempted. In this case the hydroxymethyl group of the dihydropyran LXV would supply the alcohol, thus requiring only the addition of bromine (Chart 63).

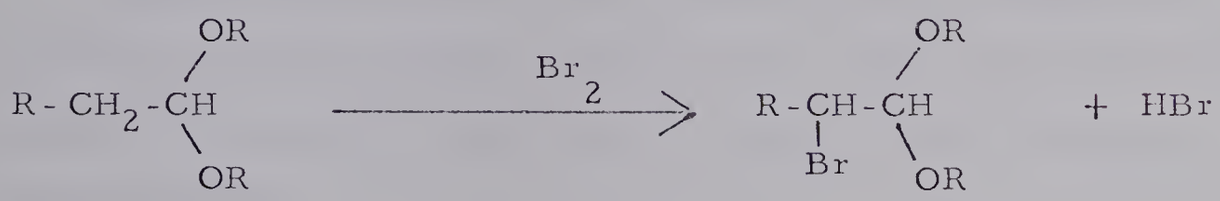


LXV LXVII

CHART 63

However this route was unsuccessful since all attempts at bromoalkoxylation produced only intractable, resinous material.

The bromination of acyclic acetals is known (79) to produce



α-bromoacetals* in variable yields. It was therefore reasoned that compound LXVI, which possesses an acetal function with an unsubstituted α-position (C-4, bicyclo numbering) should undergo a similar reaction with bromine.

Accordingly LXVI was treated with bromine in carbon tetrachloride at 35°, in the presence of sodium carbonate. From the

* It is interesting to note that α-bromination of acetals is reported to proceed in equally good yields under alkaline (79) and acid (104) conditions.

reaction was obtained the distillable liquid 4-bromo-6,8-dioxabicyclo-[3·2·1] octane (LXVII) in yields of 60-75% (Chart 64)*.

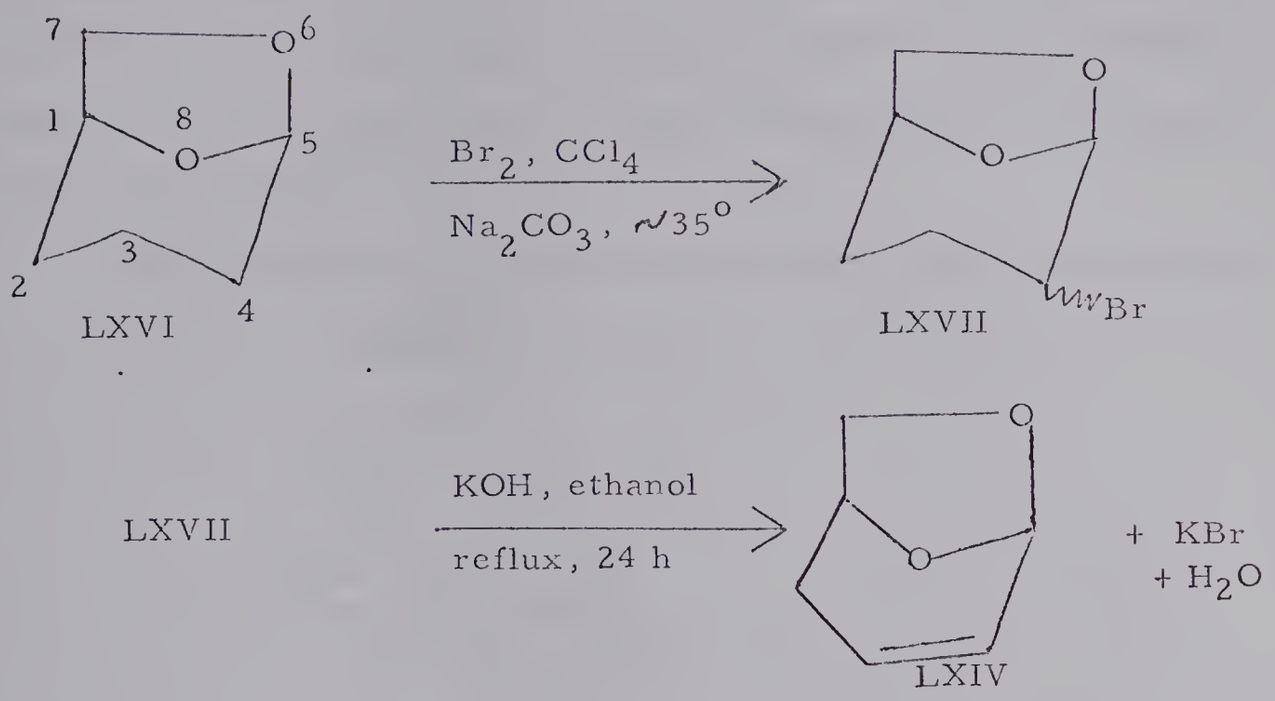


CHART 64

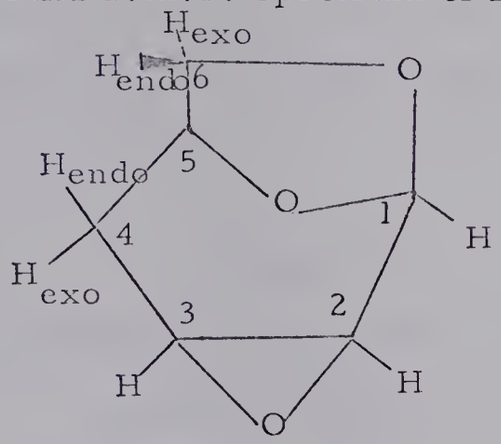
Dehydrobromination of LXVII with hot alcoholic potassium hydroxide proceeded sluggishly and gave only a 30% conversion of the bromide to the distillable olefin LXIV, along with 65% of recovered starting material.

The olefin LXIV was treated with m-chloroperoxybenzoic acid, under conditions similar to those described in Chapters IV and VII (cf. Chart 61), to give an 80% yield of epoxide LX containing a small

* G.l.c. analysis on a column that separates cis and trans 2-alkoxy-3-bromotetrahydropyrans showed one symmetrical peak for LXVII. The 100 MHz n.m.r. spectrum of LXVII shows one sharp singlet for H-1. It is therefore felt that in the bromination reaction represented in Chart 64 (LXVI ⟶ LXVII) only one C-4 Br isomer is formed. The very slow dehydrohalogenation of the bromide (LXVII) tends to indicate that the bromine atom is in the equatorial position (see Chapter VII).

amount (< 5%) of a contaminant. This contaminant was considered to be the cis isomer (LXII) of LX since elemental analysis of the mixture of LX plus the contaminant was correct for LX. The n.m.r. spectrum as well as the known (Chapters IV and VII) stereochemical course of the epoxidation reaction support the structure LX assigned to the major product.

The 100 MHz n.m.r. spectrum of LX (Fig. 18) (contaminated



by < 5% of the isomer) showed two signals in the anomeric (H-1) region in the area ratio of > 95: <5. The presence of the contaminant is shown by the low intensity doublet at τ4.25 ($J_{1,2}$=3.3 Hz) in the anomeric proton region of the spectrum of LX. This small amount of contaminant offered no complication in the first order analysis of the spectrum. That the intense singlet at τ 4.36 is due to the anomeric proton of the DL-ribo-hexopyranose, LX, while the low intensity doublet at τ4.25 is due to the anomeric proton of the lyxo isomer is in accordance with the finding that when H-2 of the epoxy ring of 1-alkoxy-2,3-epoxytetrahydropyrans* is trans to H-1 the

* Here we are numbering the tetrahydropyran ring so that the carbon atom adjacent of the ring oxygen and attached to the alkoxy group is #1, in accordance with the practice for the pyranosides. This is done as a matter of convenience.

anomeric proton (H-1) signal is a singlet with H-1 , H-2 coupling ~ 0. If H-1 and H-2 are cis , the coupling $J_{1,2} = 2.5$ to 4.5 Hz (72) (Chapter IV , Section C).

The obvious signal assignment is that of the "singlet" at τ 4.36 for the anomeric proton H-1. The two quartets at high field centered at τ 7.57 and τ 8.33 can be assigned reasonably to the two protons on C-4. Using the C-1 and C-4 protons as reference points , signal assignments (Table VI) can be made by decoupling experiments. These are described below.

TABLE VI

Observed Chemical Shifts of Protons in LX ,

(obtained in $CDCl_3$ at 100 MHz)

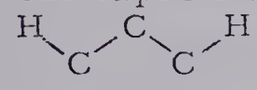
H-1	H-2	H-3	H-4-exo	H-4-endo	H-5	H-6-exo	H-6-endo
4.36s	7.03d	6.83m	7.57q	8.33q	5.56m	6.08m	6.25m
			AB system			AB system	

(s= singlet; d= doublet , q=quartet; m=multiplet)

Irradiation of H-1 gave a small but definite collapse of the signals at τ 7.03 and τ 6.83 , tentatively identifying these as due to H-2 and H-3. On the basis of work previously discussed in Chapter IV the higher field signal is due to H-2. Irradiation at τ 7.03 (H-2) gave some sharpening of the H-1 signal at τ 4.36. A collapse of a small coupling occurred at the low field C-4 proton quartet (τ 7.57), but there was no effect on the high field C-4 proton quartet (τ 8.33).

On the other hand, irradiation at τ 6.83 (tentatively assigned to H-3), change the high field quartet (C-4 proton, τ 8.33) to a doublet of 15.8 Hz, but left the lower field H-4 quartet intact. This information clearly shows that the H-3 signal is the multiplet at τ 6.83 since strong coupling is expected between H-3 and a C-4 proton. Thus the signal at τ 7.03 is due to H-2.

A tentative assignment of the two high field quartets to the two protons on C-4 can now be made by using the Karplus relation between the size of the dihedral angle and the magnitude of the coupling (45). From the rigid structure of LX, it is seen that the H-3, H-4 exo dihedral angle is very nearly 90° while that for H-3, H-4 endo is nearly 30°. Thus a larger coupling is expected for H-3, H-4 endo than for H-3, H-4 exo. On this basis, in keeping with the above information, the high-field quartet at τ 8.33 is assigned to H-4 endo and therefore that at τ 7.57 is due to H-4 exo.

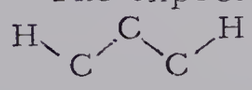
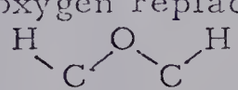
Irradiation at τ 7.57 (H-4 exo) causes a pronounced change of the multiplet at τ 5.56, identifying this as due to H-5. As well, small couplings disappear in the τ 6.08 region, but little if any change occurs at τ 6.25. Since one expects a long range coupling between protons which have the  configuration (99), the clearly noticeable small change at τ 6.08 indicates that this multiplet is due to H-6 exo, leaving the τ 6.25 region for H-6 endo. Some observable change also occurred at τ 6.83 (H-3).

Irradiation at τ 5.56 (H-5) caused a collapse of the quartet at τ 7.57 (H-4 exo) to a doublet, but relatively little change at τ 8.33 (H-4 endo). The former confirms the assignment of the multiplet at

τ5.56 to H-5. The larger coupling of H-5 to H-4 exo, but apparently little coupling of H-5 to H-4 endo, agrees with the prediction from the Karplus relation (45), since the dihedral angle for H-5, H-4 exo $\sim 40^{\circ}$ while that for H-5, H-4 endo $\sim 80^{\circ}$.

Irradiation of the region τ 6.15 (H-6 exo) gave collapse of the small couplings at τ 7.57 (H-4 exo). This corroborates the view that the signal at τ6.08 is due to H-6 exo.

To determine the degree of coupling between the protons, 100 Hz sweeps were made of portions of the spectrum while suitably chosen protons were irradiated. In this manner it was possible to obtain coupling constants for nearly all of the protons. These are shown in Table VII. The expanded signals and the first order couplings are shown in Figs. 19 and 20.

The data in Table VII shows that H-1 is coupled to all other protons with the exception of H-4 exo. The H-4 endo and H-6 endo protons are at slightly higher field, and thus subjected to more shielding, than are H-4 exo and H-6 exo. The expected long range coupling between protons which have the  structure is clearly discernible, but in addition, such long range coupling is found when oxygen replaces one of the carbon atoms in this structural feature, i.e. . An example of long range coupling over 5 bonds (100) is shown in the coupling between H-1 and H-4 endo.

The above n.m.r. information agrees with the structural assignment of LX as the major product obtained from epoxidation of the olefin XLIV (Chart 61).

Treatment of the epoxide LX (Chart 60) with boiling 5% aqueous

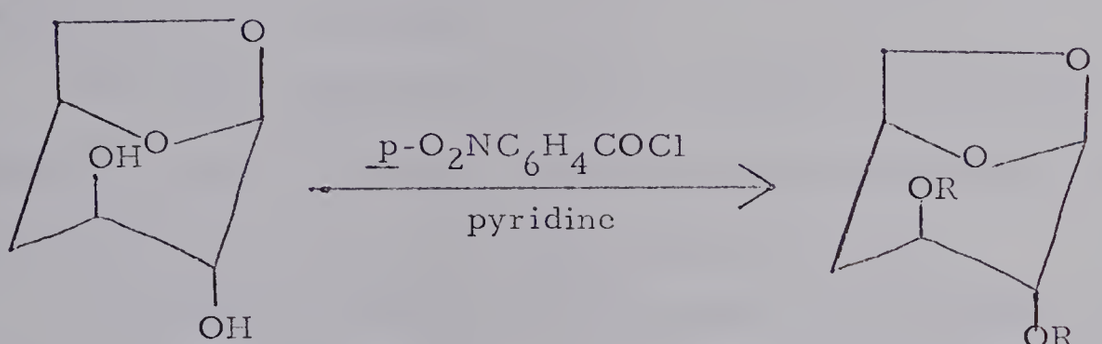
TABLE VII

Observed Coupling Constants of Protons in LX.

(Hz)

	H-1	H-2	H-3	H-4 exo	H-4 endo	H-5	H-6 exo	H-6 endo
H-1		1.0	0.7	0	0.5	0.4	0.4	0.4
H-2			4.0	0.9	0			
H-3				0.3	5.2	1.8		
H-4 exo					15.8	4.8	1.4	0.4
H-4 endo						0.8	0	0
H-5							5.8	2.3
H-6 exo								7.7

potassium hydroxide by the method of Černý et al (96, a and b) gave in 70% yield a solid which melted at 155-156°. Elemental analysis and the n.m.r. spectrum (Fig. 21) of the solid supports the structure DL-LXI. The carbohydrate of the D-series, LXI, obtained by Černý (96) had a reported melting point of 155-157°. The apparent agreement between these melting points must be treated with caution since one cannot tell a priori whether the DL-mixture is a racemic compound or merely a racemic mixture, or what the melting point of the DL mixture should be. Hence the similarity of melting points in this case might be merely a fortunate coincidence. Up to the time of the present work, a DL mixture of LXI had not been prepared. It is interesting that the di-p-nitrobenzoate DL-LXVIII (m.p. = 198°) prepared from DL-LXI, melts about 20° below that of the correspond-



DL-LXI R = p-$O_2NC_6H_4CO$ DL-LXVIII

ing derivative (96) of D-LXI (m.p. = 218°).

Convincing evidence concerning the structure of DL-LXI was obtained from n.m.r. analysis of its di-p-nitrobenzoate DL-LXVIII (Fig. 22). The 100 MHz n.m.r. spectrum of an authentic sample of the di-p-nitrobenzoate (D-LXVIII) derivative of D-LXI* in $CDCl_3$

* The author is indebted to M. Černý for making available authentic samples of 1,6-anhydro-4-deoxy-β-D-xylo-hexopyranose di-p-nitrobenzoate, as well as 1,6-anhydro-4-deoxy-β-D-arabino-hexopyranose (LXIII) and its di-p-nitrobenzoate derivative.

solution was superimposable on the 100 MHz spectrum of the di-p-nitrobenzoate of the DL mixture of LXI. The n.m.r. spectra of the di-p-nitrobenzoates of the D enantiomers of LXI and LXIII are clearly different from each other.

The chemical evidence for assigning the structure DL-LXI to the sugar obtained in this laboratory rests partly on the findings (Chapters IV and VI) that pyranyl epoxide rings open almost exclusively at the carbon remote from the anomeric center. Furthermore, Černý et al found (96b) that treatment of D-LX with aqueous base leads exclusively to D-LXI, as was pointed out above. These authors also reported (96b) that similar treatment of D-LXII gave a mixture of D-LXI and D-LXIII (Chart 60). In the present work treatment of DL-LX (contaminated with $< 5\%$ of DL-LXII) with hot aqueous alkali produced only one compound.

The above chemical and n.m.r. evidence supports the suggestion that a DL mixture of LXI has been successfully prepared in this laboratory from non-carbohydrate precursors.

It is believed that the work described in this chapter and that of Chapter VII are the first reported syntheses of 4-deoxy hexopyranoses accomplished by stereoselective elaboration of a monosubstituted pyran ring.

SPECTRA

Unless otherwise stated all n. m. r. spectra were obtained in deuteriochloroform and the reference was tetramethylsilane.

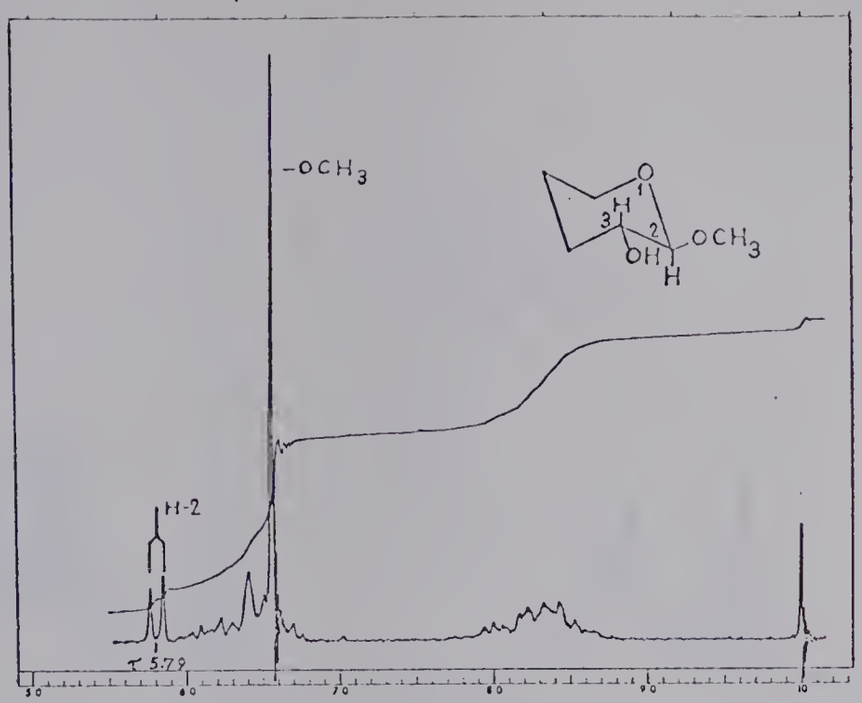


FIGURE 1 (a) N.m.r. spectrum (60 MHz) of trans-3-hydroxy-2-methoxytetrahydropyran.



FIGURE 1 (b) N.m.r. spectrum (60 MHz) of cis-3-hydroxy-2-methoxytetrahydropyran.

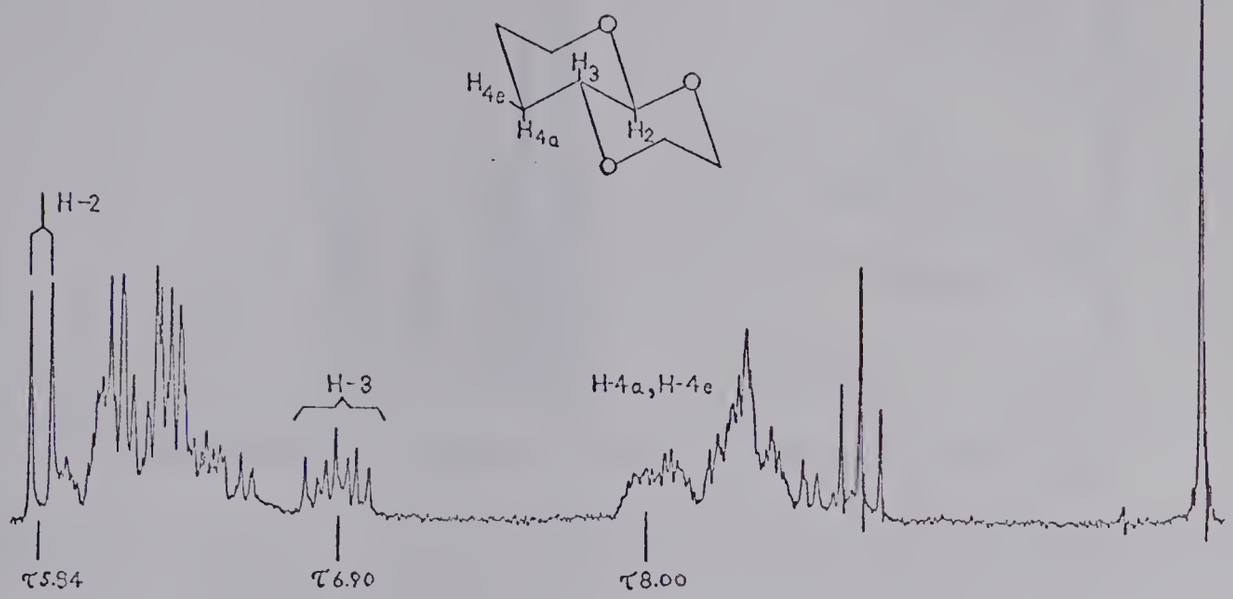


FIGURE 2. N.m.r. spectrum (100 MHz) of trans-tetrahydropyrano-[2,3-b]-1,4-dioxane.

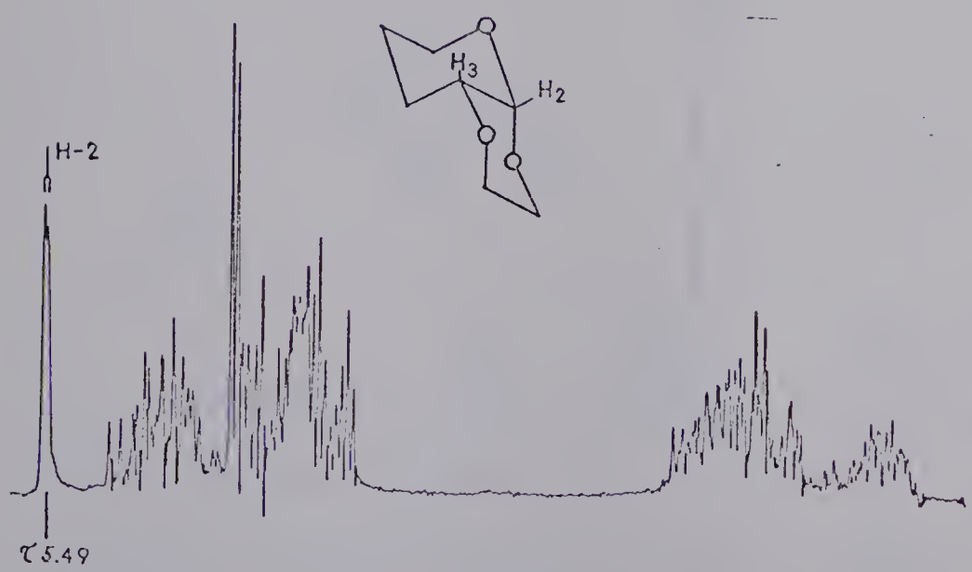


FIGURE 3. N.m.r. spectrum (100 MHz) of cis-tetrahydropyrano-[2,3-b]-1,4-dioxane.

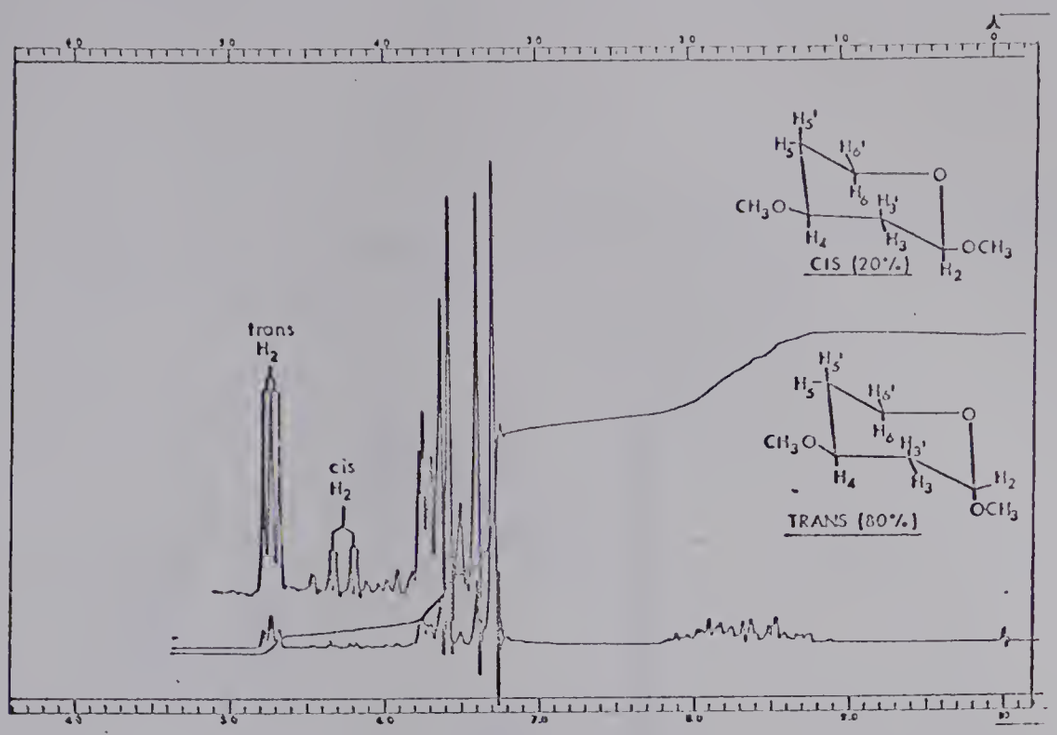


FIGURE 4. N.m.r. spectrum (60 MHz) of cis, trans-2,4-dimethoxy-tetrahydropyran.

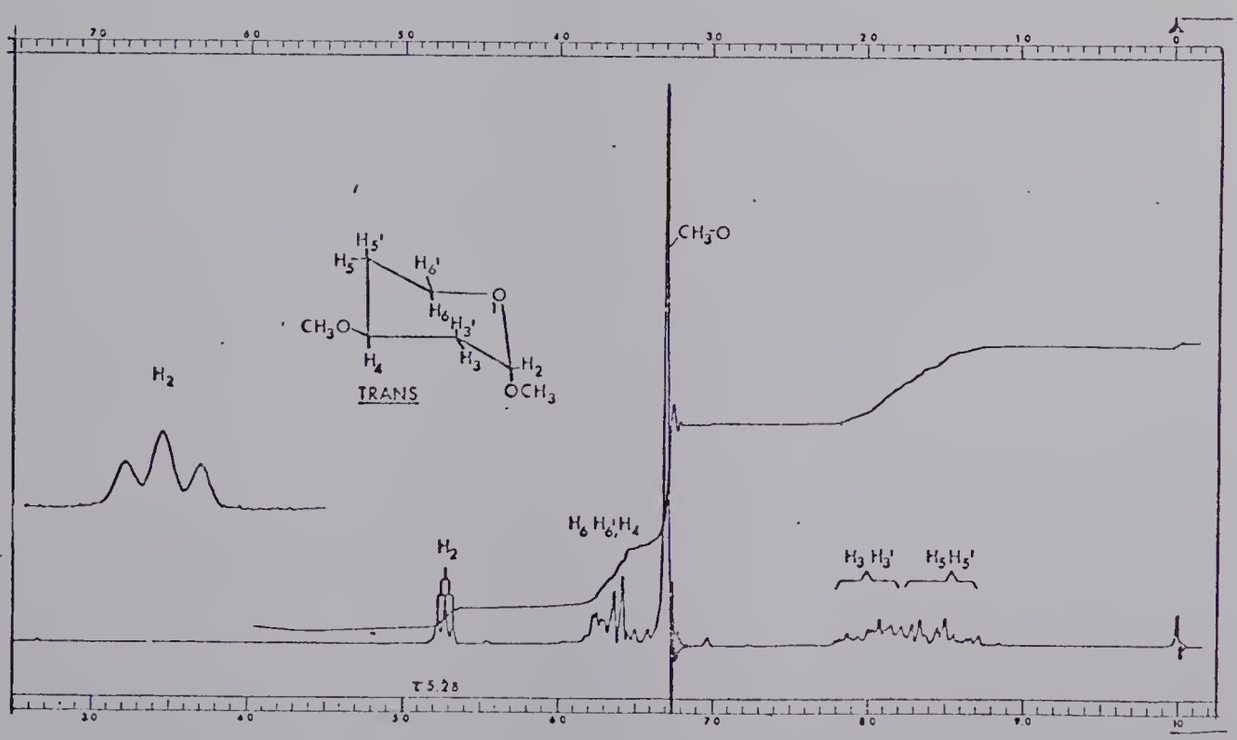


FIGURE 5. N.m.r. spectrum (60MHz) of trans-2,4-dimethoxy-tetrahydropyran.

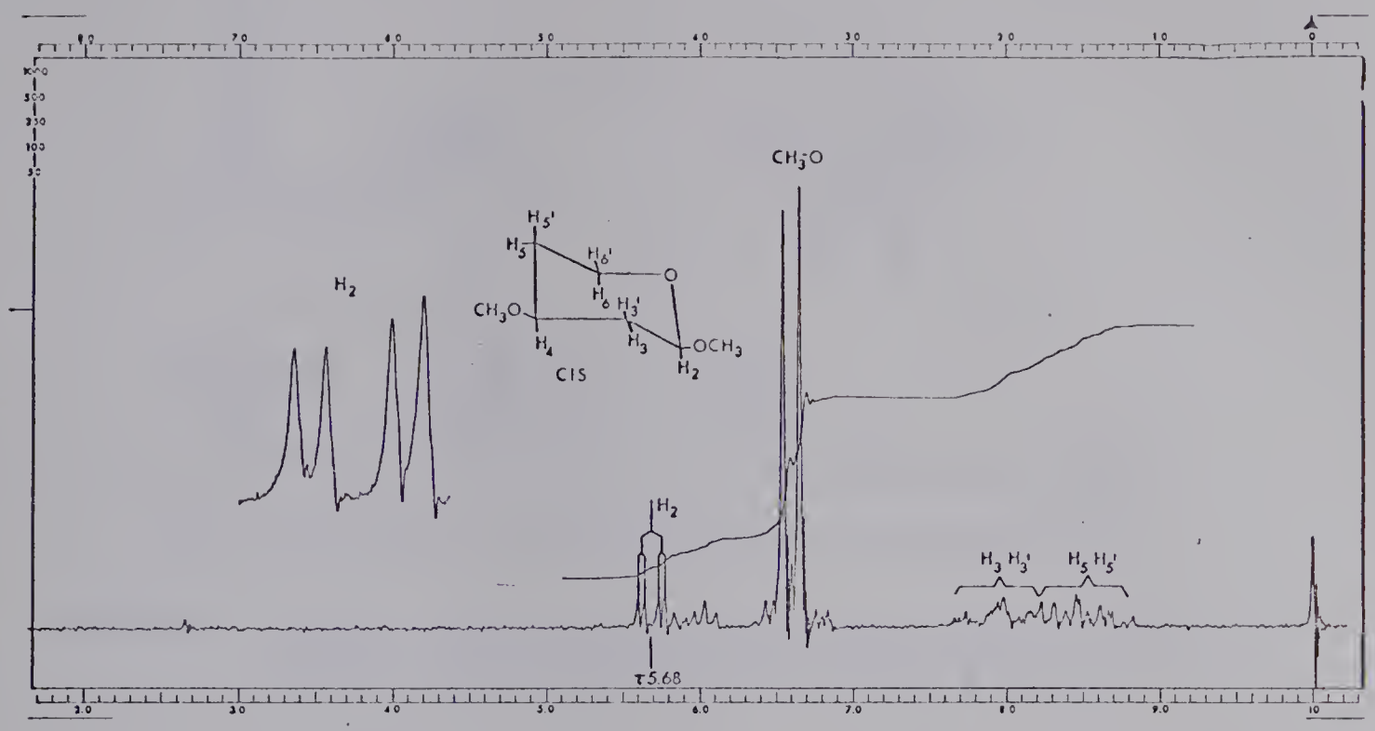


FIGURE 6. N.m.r. spectrum (60 MHz) of cis-2,4-dimethoxytetrahydropyran.

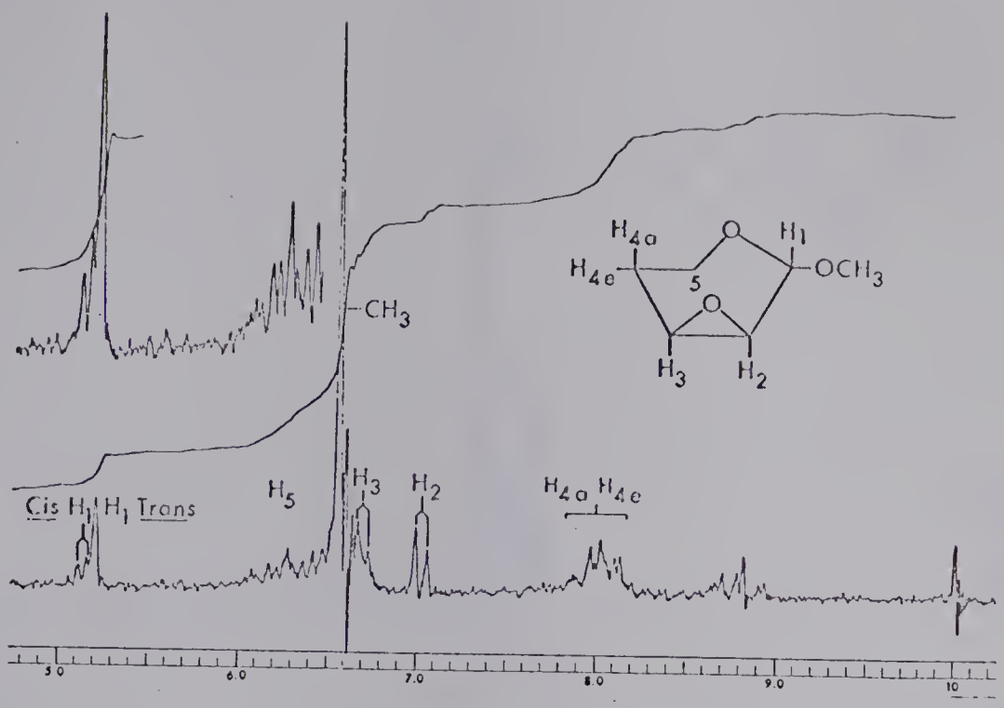


FIGURE 7. N.m.r. spectrum (60 MHz) of cis,trans-3,4-epoxy-2-methoxytetrahydropyran (XXXVII, a and b).

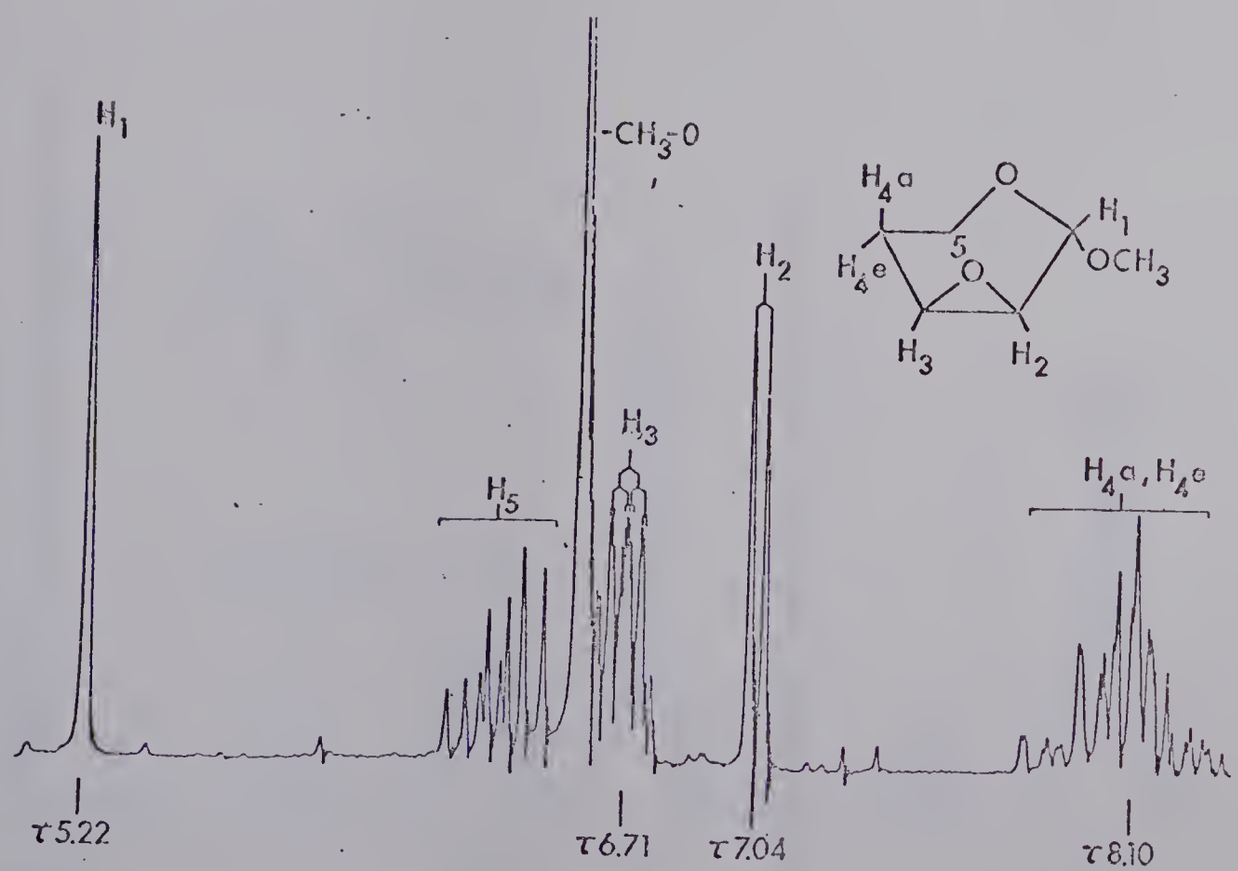


FIGURE 8. N.m.r. (100 MHz) of trans-3,4-epoxy-2-methoxytetrahydropyran (XXXVIIa).

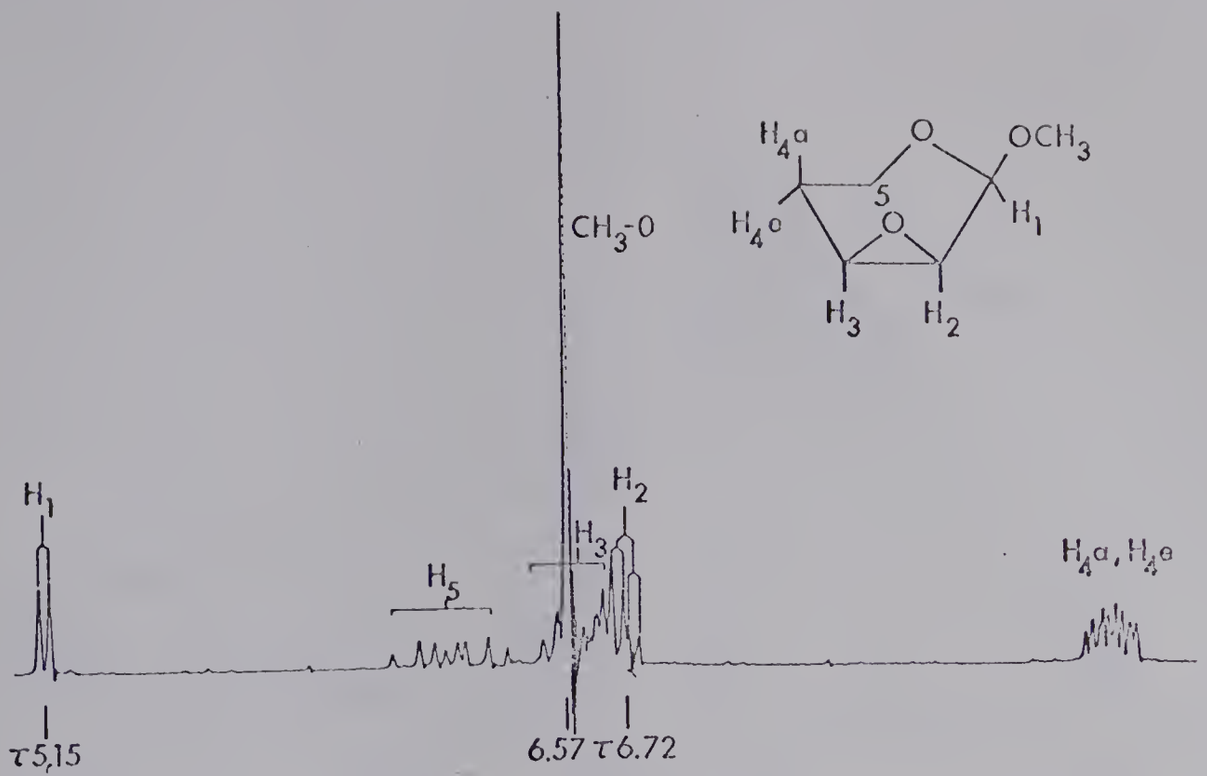


FIGURE 9. N.m.r. spectrum (100 MHz) of cis-3,4-epoxy-2-methoxy-tetrahydropyran (XXXVII b).

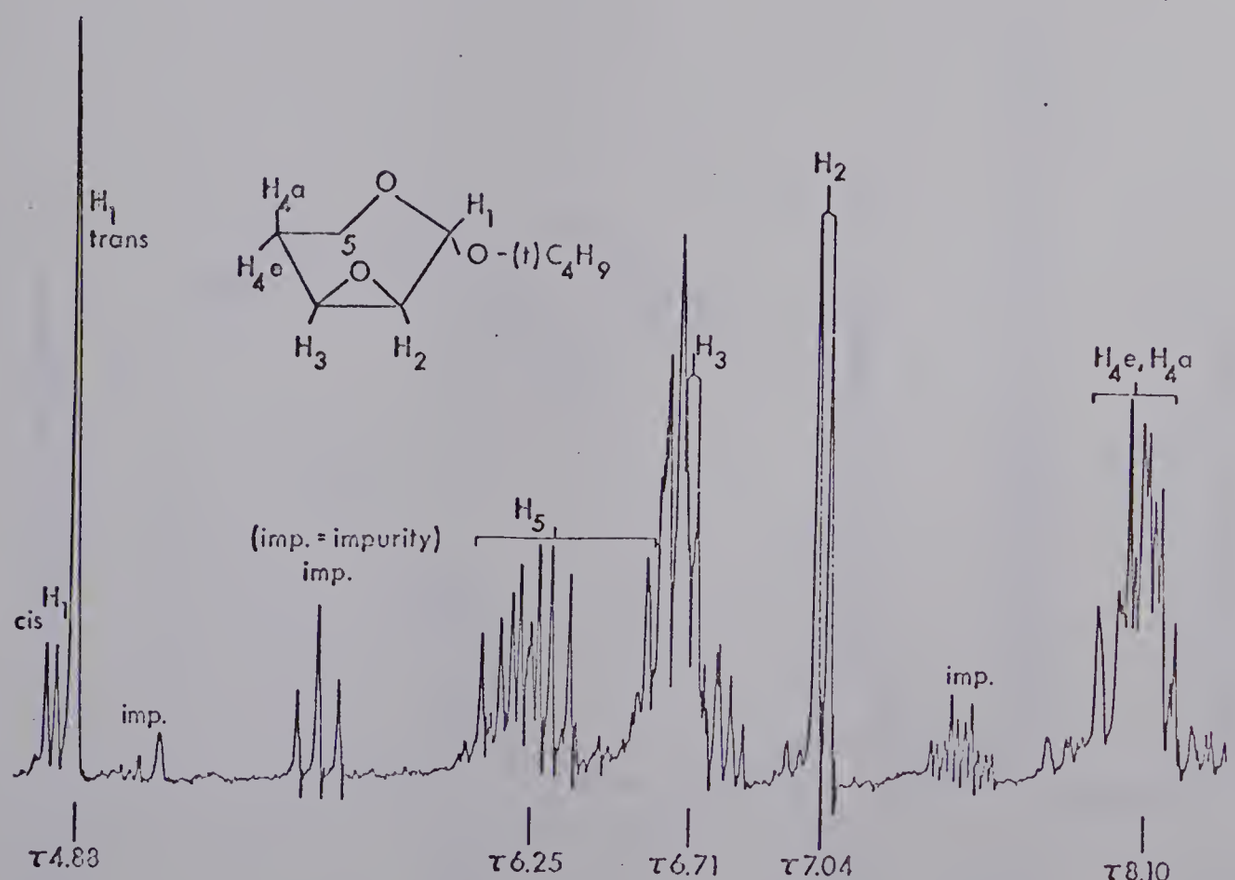


FIGURE 10. N.m.r. spectrum (100 MHz) of trans-2-t-butoxy-3,4-epoxytetrahydropyran (XXXVIII).

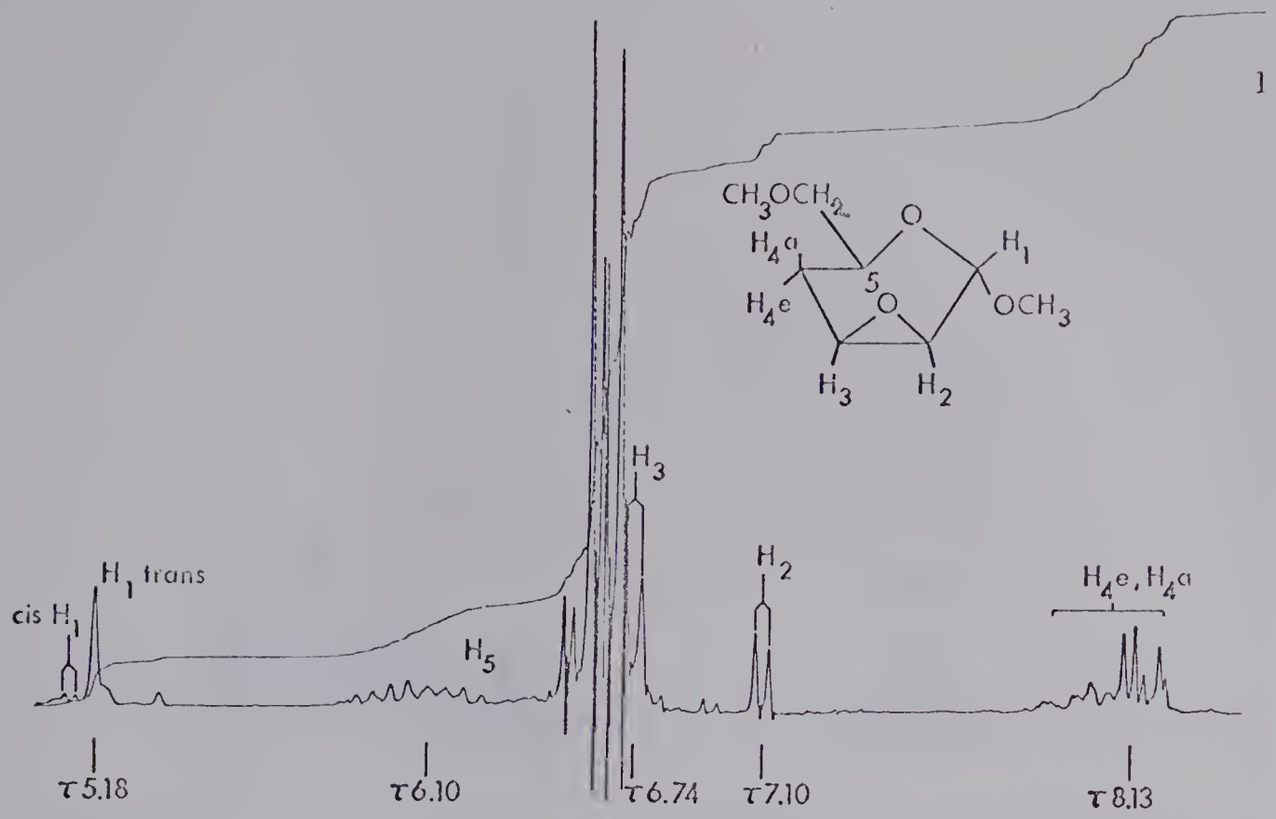


FIGURE 11. N.m.r. spectrum (100 MHz) of methyl 2,3-anhydro-4-deoxy-6-O-methyl-α-DL-lyxo-hexopyranoside (XXXIX or LVII).

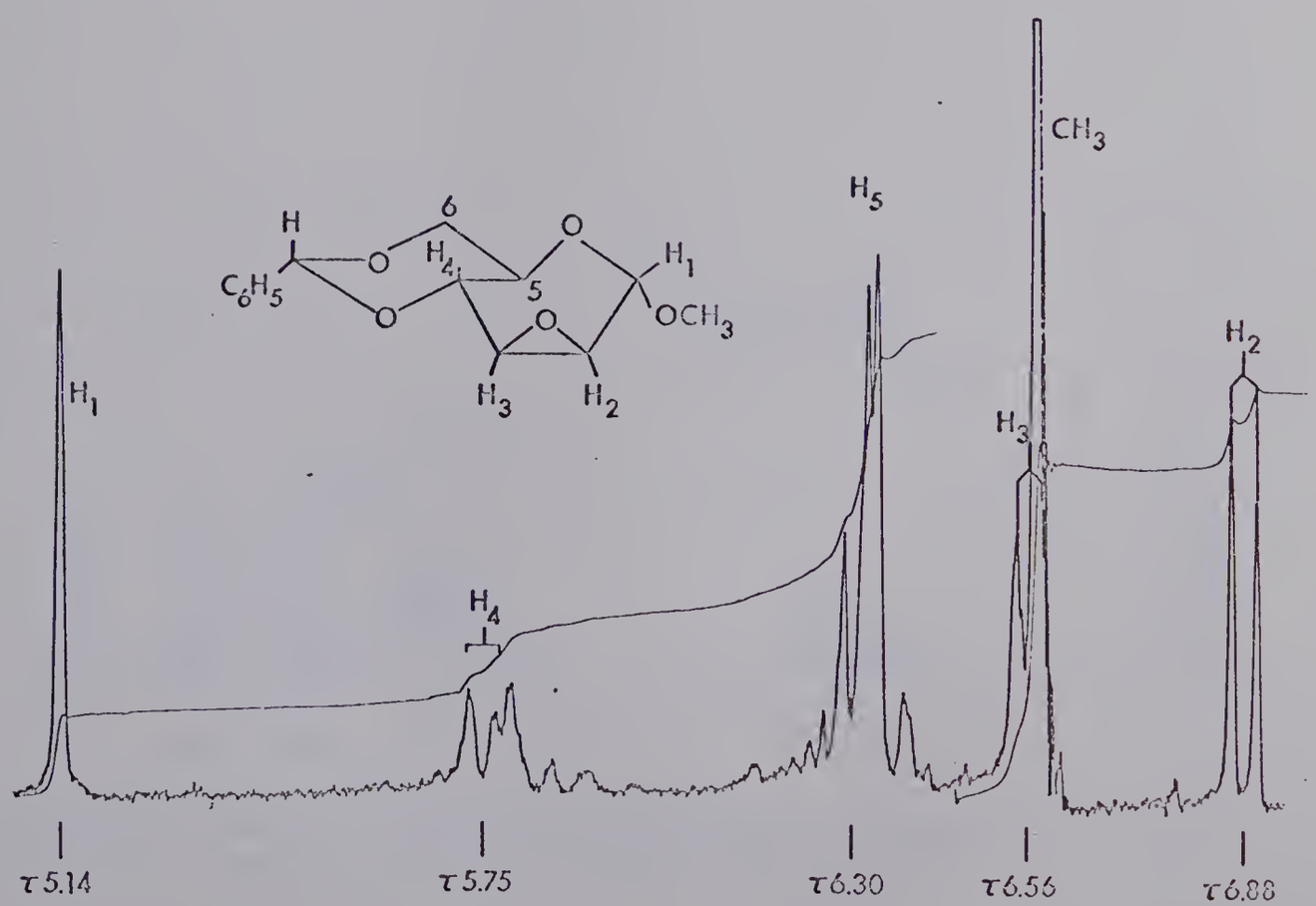


FIGURE 12. N.m.r. spectrum (100 MHz) of methyl 4,6-O-benzylidene-2,3-anhydro-α-D-mannopyranoside (XL).

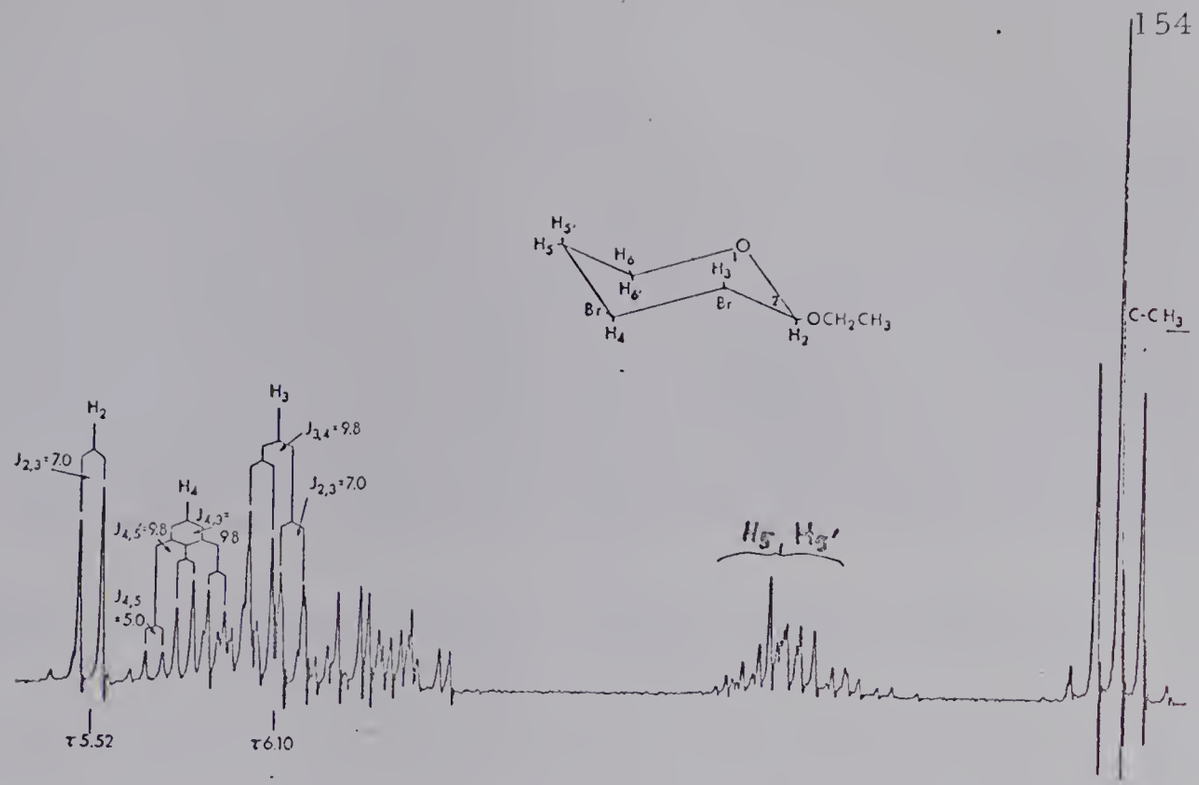


FIGURE 13. N.m.r. spectrum (100 MHz) of 3,4-dibromo-2-ethoxy-tetrahydropyran (solid isomer, XLIIa).

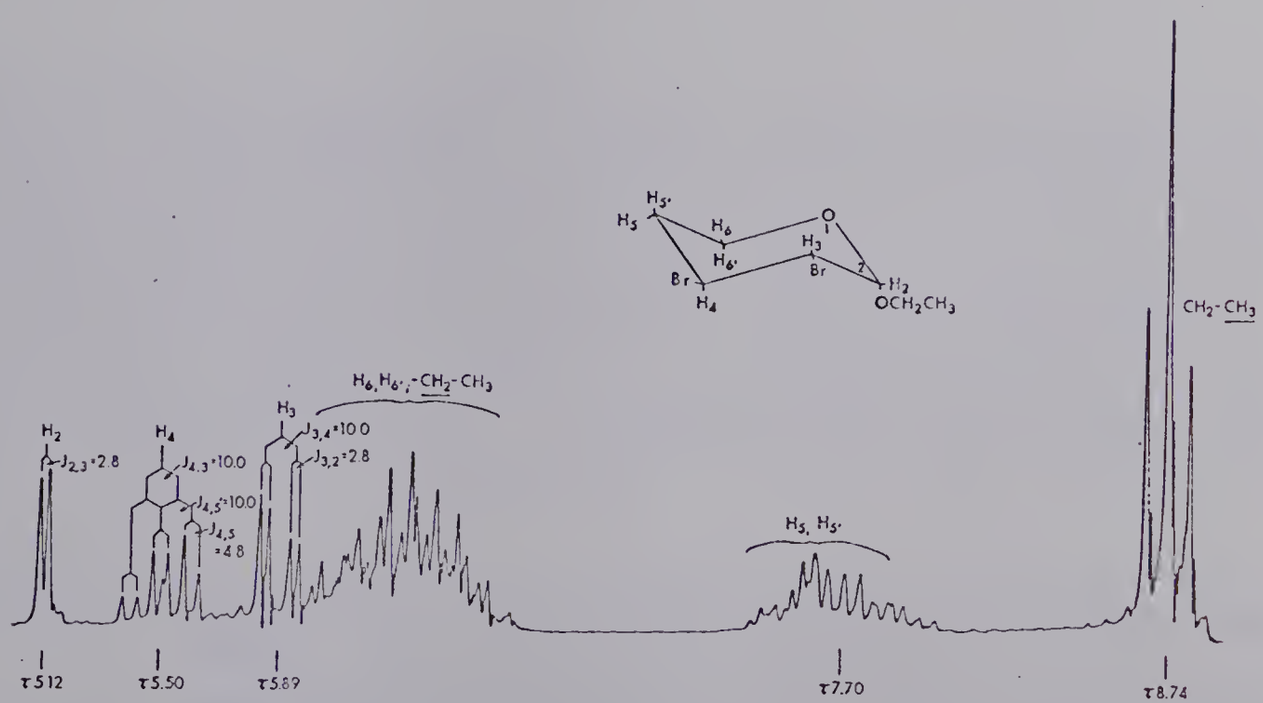


FIGURE 14. N.m.r. spectrum (100 MHz) of 3,4-dibromo-2-ethoxy-tetrahydropyran (liquid isomer, XLIIb).

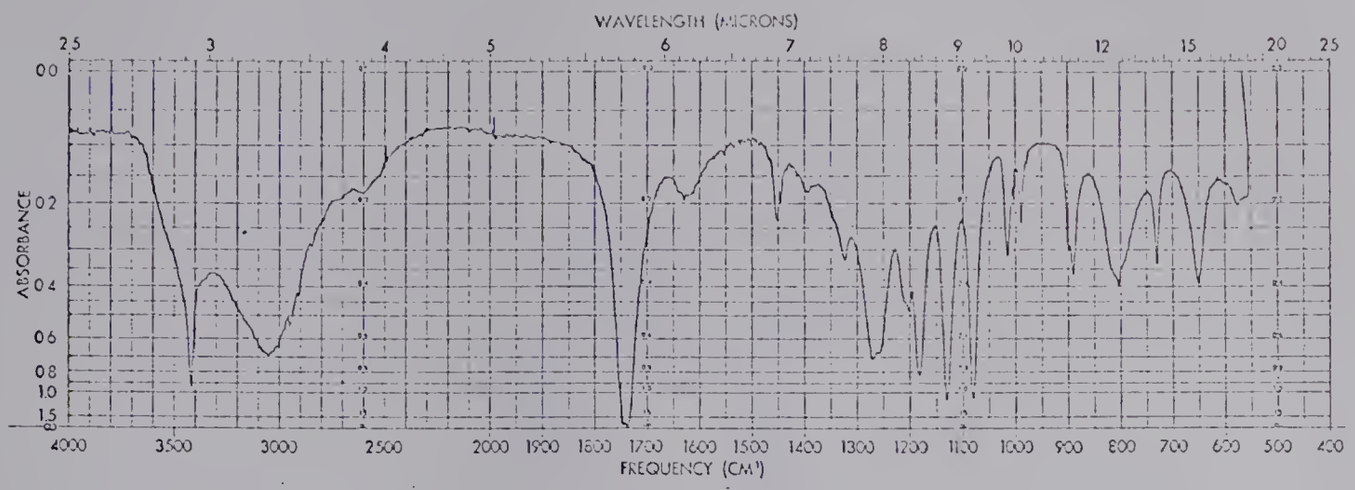


FIGURE 15. I.R. spectrum of O-methyl-DL-tartaric acid (m.p., 196-202°, dec.). (KBr pellet).

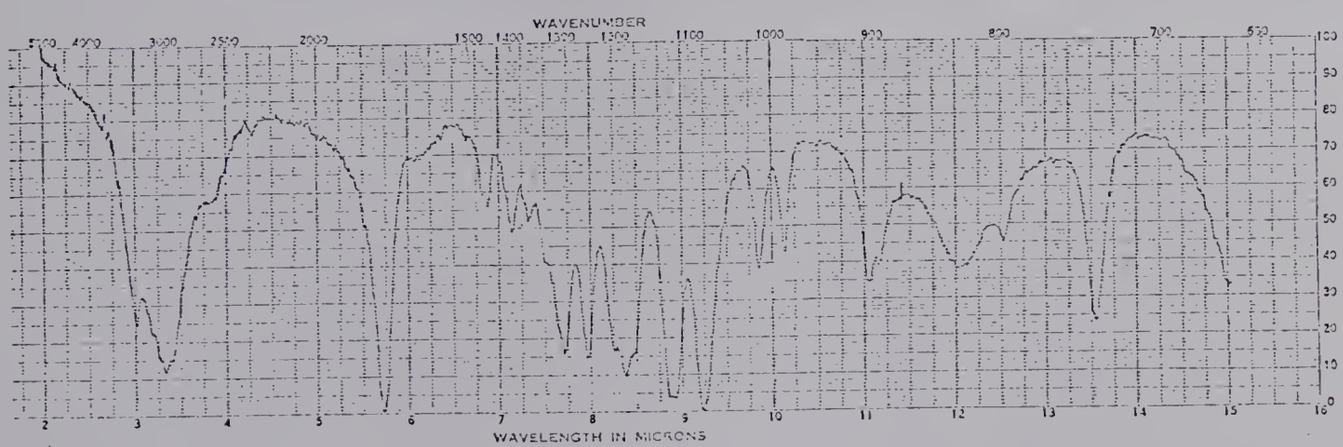


FIGURE 16. I.R. spectrum of O-methyl-L-tartaric acid (m.p., 179-182°, dec.). (Spectrogram is linear in wavelength. KBr pellet). (This sample and the infrared spectrum were generously donated by Dr. P. W. K. Woo of Parke, Davis and Company, Detroit Michigan.)

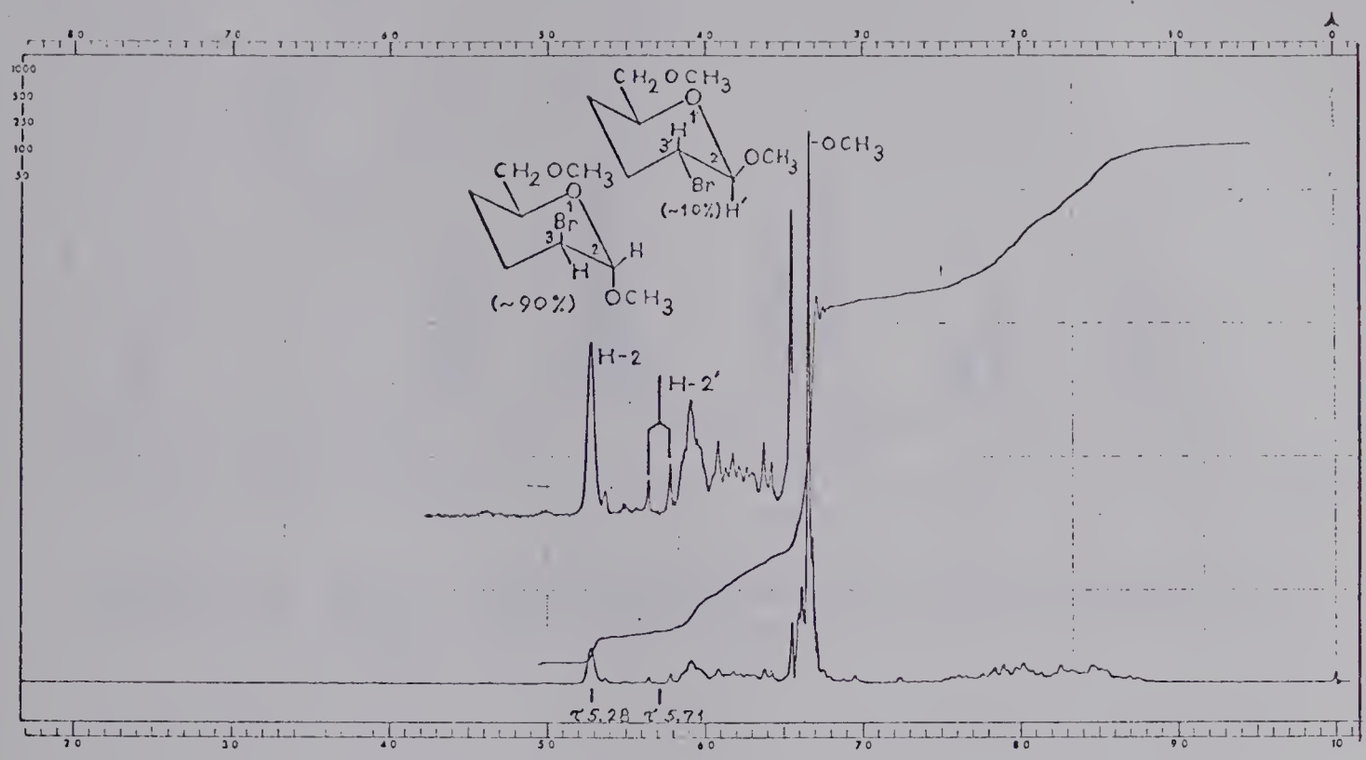


FIGURE 17. N.m.r. spectrum (60 MHz) of isomeric 3-bromo-2-methoxy-6-methoxymethyltetrahydropyran (LIII and LIV).

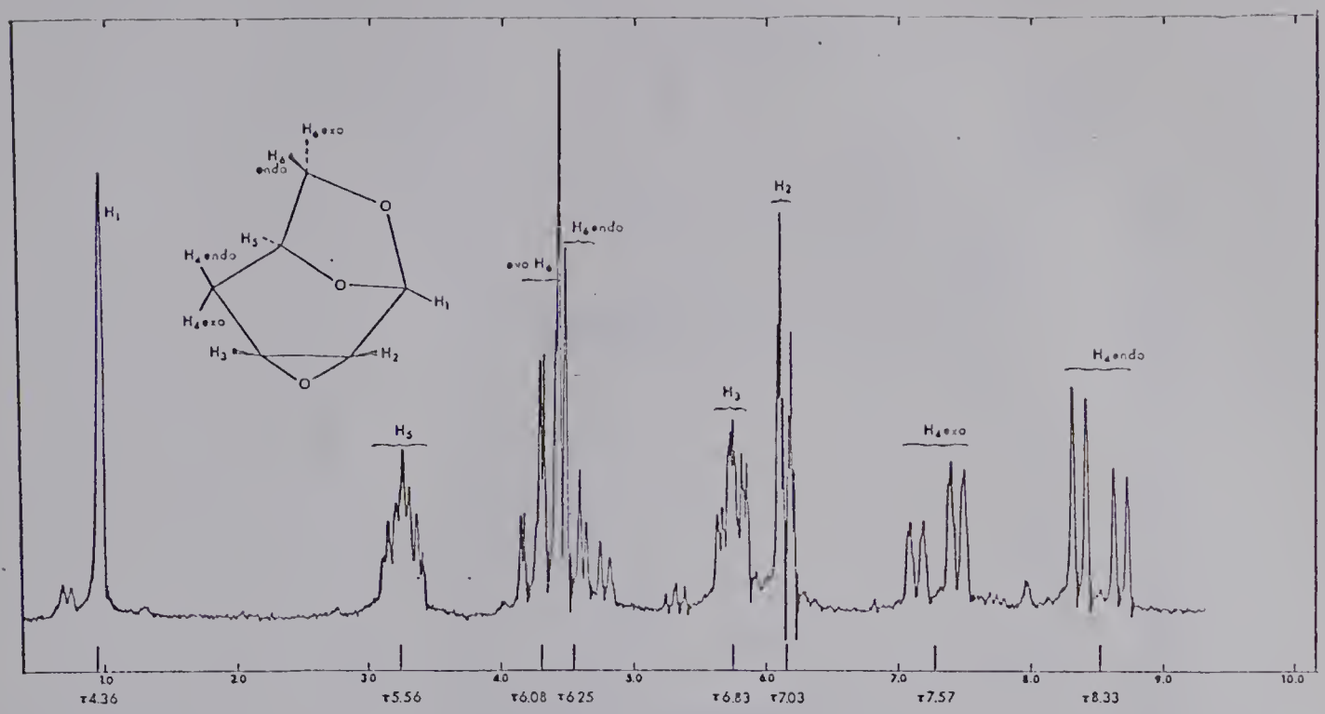


FIGURE 18. N.m.r. spectrum (100 MHz) of 1,6:2,3-dianhydro-4-deoxy-β-DL-ribo-hexopyranose (LX).

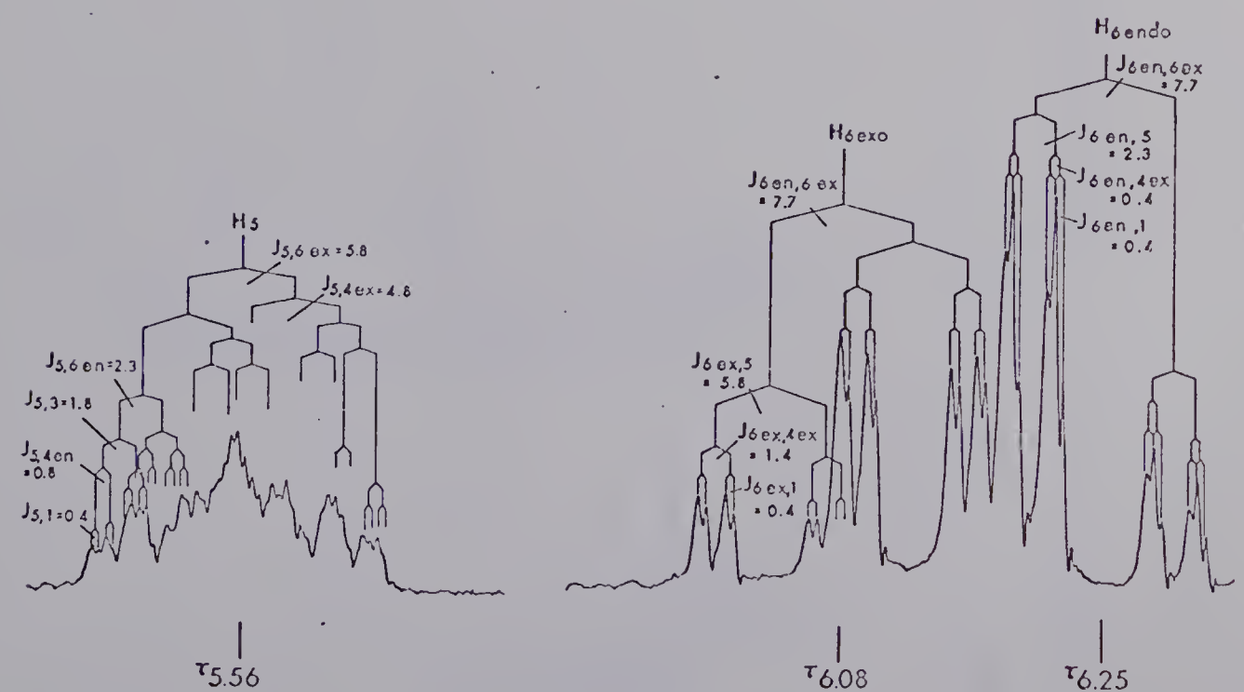


FIGURE 19. N.m.r. spectrum (100 MHz) of H-5, H-6 exo, and H-6 endo in LX.

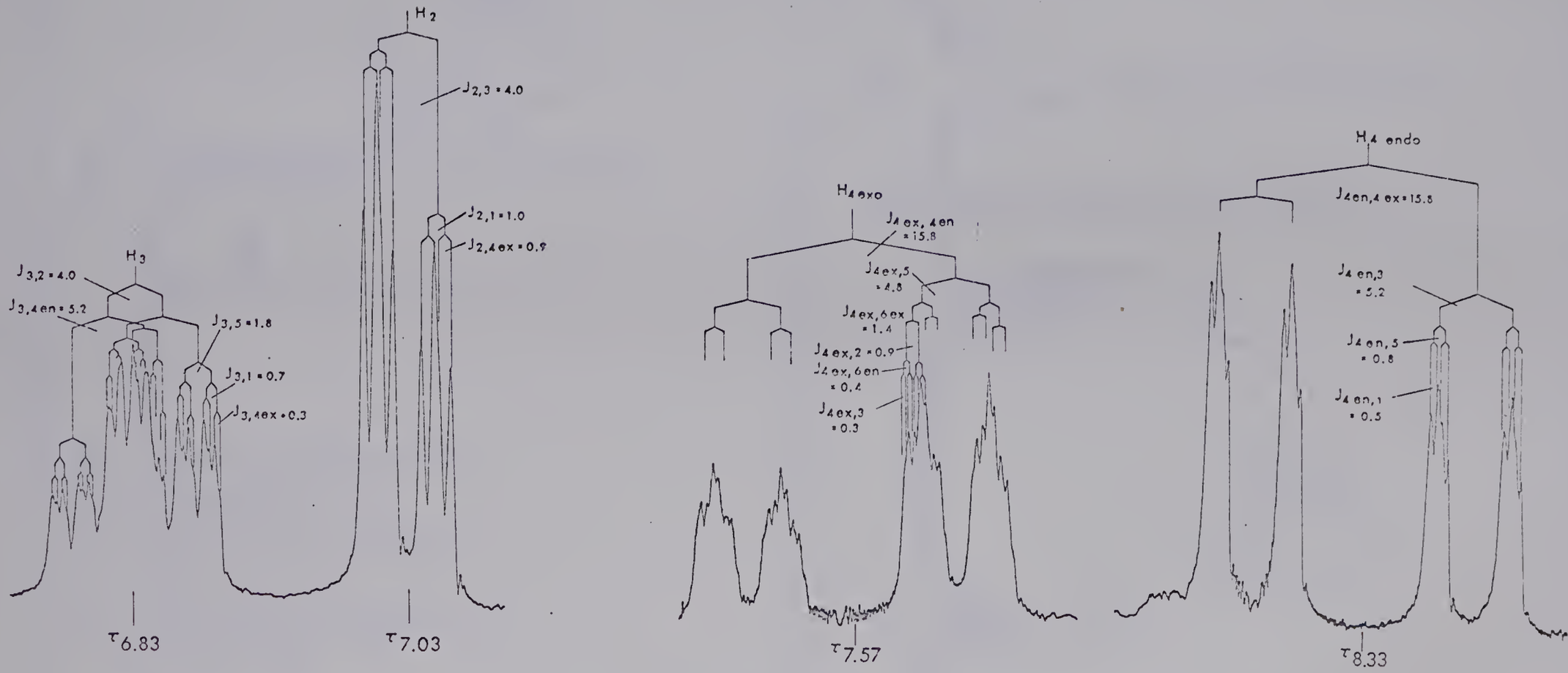


FIGURE 20. N.m.r. spectrum (100 MHz) of H-3, H-2, H-4 exo, and H-4 endo in LX.

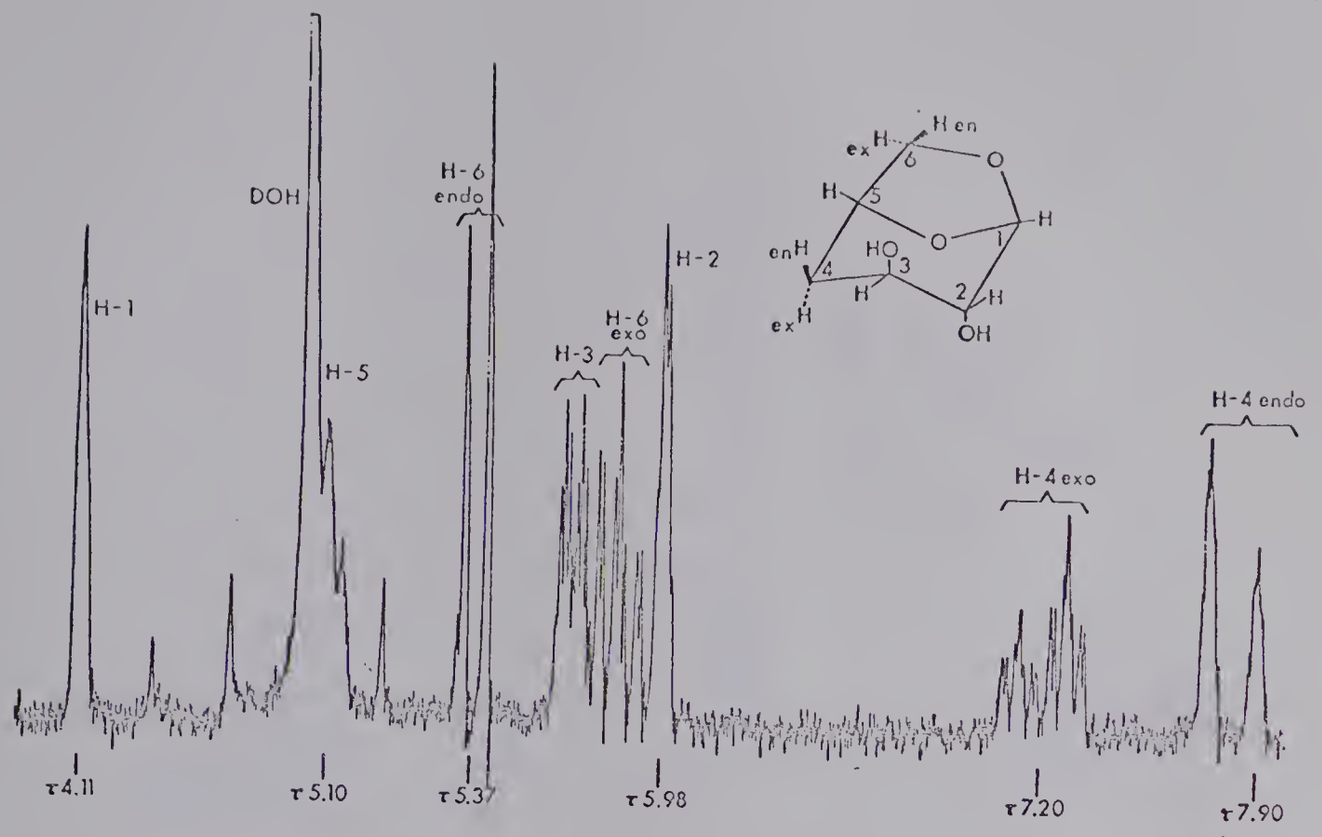


FIGURE 21. N.m.r. spectrum (100 MHz) of 1,6-anhydro-4-deoxy-β-DL-xylo-hexopyranose (LXI) (in deuterium oxide).

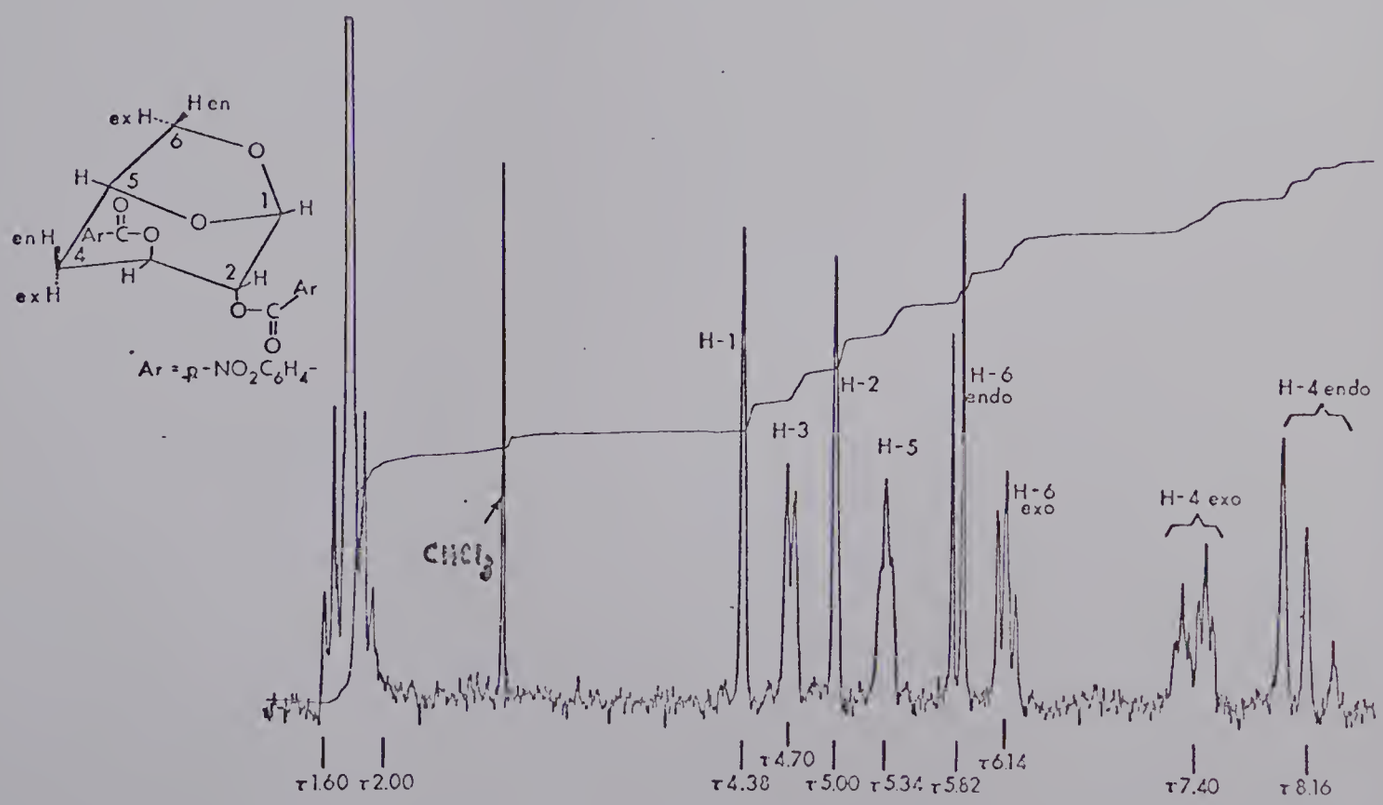


FIGURE 22. N.m.r. spectrum (100 MHz) of 1,6-anhydro-4-deoxy-β-DL-xylo-hexopyranose di-p-nitrobenzoate.

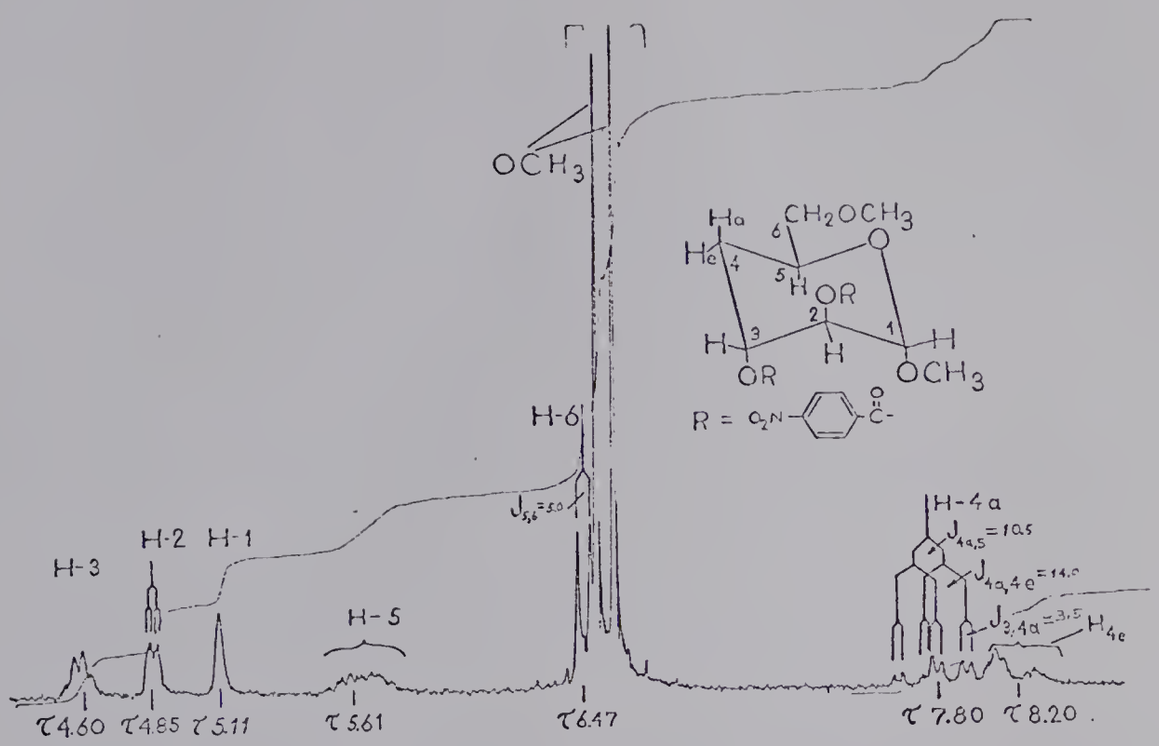


FIGURE 23. N.m.r. spectrum (100 MHz) of methyl 4-deoxy-6-O-methyl-α-DL-arabino-hexopyranoside di-p-nitrobenzoate.

EXPERIMENTAL

All boiling points and melting points are uncorrected.

Fractional distillations were generally carried out with the Nestor-Faust spinning band column. In some cases the temperature of the heating bath at the time of distillation is indicated in parenthesis immediately following the boiling point. This is done to facilitate reproduction of the distillation conditions.

Gas-liquid chromatography (g. l. c.) was performed with one or more of the following machines:

(a) Burrell K-2 Kromo-Tog equipped with a standard 2. 5 meter U-shaped glass column. The column packing used was 20% butanediol succinate supported on Gas-chrom P (60-80 mesh). Helium, at a flow rate of 70 ml per minute, was used as the carrier gas.

(b) Fand M model 700 gas liquid chromatograph equipped with 1/8" x 12' stainless steel columns. Two column packings were used which generally gave good separation of isomeric acetals, alcohols and substituted tetrahydropyrans (i) 20% butanediol succinate on Gas Chrom-P (60-80 mesh) and (ii) 25% carbowax 20 M on Gas Chrom-P (60-80 mesh). Helium was the carrier gas used at a flow rate of 40 ml per minute.

peak areas corresponding to the various components in a mixture. These areas were compared with those obtained from carefully prepared mixtures of authentic samples analyzed under identical conditions. Where possible the g. l. c. analyses were corroborated with results obtained from nuclear magnetic resonance (n. m. r.) spectra of the same mixtures.

Infrared spectra were recorded with a Perkin-Elmer Model 421 instrument.

N. m. r. spectra were obtained with a Varian Associates Model A-60 (60 MHz) spectrometer or a Varian Associates Model HA-100 (100 MHz.) spectrometer. Unless otherwise stated n. m. r. spectra were obtained of samples dissolved in $CDCl_3$. Tetramethyl silane was used as an internal reference.

Elemental analyses for carbon, hydrogen, halogens and nitrogen were done by Mrs. Darlene Mahlow in the Chemistry Department of the University of Alberta.

(c) The above chromatographs were used exclusively for analytical work. However, an Aerograph Autoprep, Model A-700 equipped with a 1/4" x 20' stainless steel column, was used for both analytical and preparative work. The packing materials used in this column were the same as those described in (b) above. Helium, as the carrier gas, was used at flow rates in the range of 100-120 ml per minute.

Analytical results were cross-checked by using the two types of column packings mentioned above. Best analytical results were obtained with the F and M machine.

The column temperatures employed for analytical and preparative g. l. c. work were variable and depended upon the boiling points of the compounds being analyzed. Generally, better separation of components could be obtained by using the linear temperature programmers which were incorporated in the F and M, and Aerograph instruments. The variable programmers permitted a large variety of temperature conditions to be used. However, good results were generally obtained under isothermal conditions.

All of the above-mentioned chromatographs were equipped with an automatic integrator, attached to the strip chart recorders. Quantitative analyses were made by measuring the integrated

I. PREPARATION OF 2-ALKOXY-3-HYDROXYTETRAHYDRO-PYRANS AND 2-ALKOXY-3-METHOXYTETRAHYDROPYRANS.

(The n. m. r. data for the 2, 3-disubstituted tetrahydropyrans described below is collected in Table I.)

Trans-3-hydroxy-2-methoxytetrahydropyran

3, 4-Dihydro-2H-pyran (21 g 0. 25 mole) was dissolved in 300 ml of dry methanol contained in a 1 l, three neck flask equipped wi condenser, magnetic stirrer and a low temperature thermometer. The flask and contents were kept between -10° and -5° with a dry ice-acetone bath, while a solution of 34. 4 g (0. 2 mole) of m-chloroperoxybenzoic acid in 50 ml of chloroform was added over a period of approximately 0. 5 h. The cooling bath was then removed and the reaction mixture was stirred overnight at room temperature. The solution was then freed from solvents in a rotary evaporator under reduced pressure (water aspirator), and the residual solid was shaken with 300 ml of chloroform. The resulting suspension was left in the refrigerator at -20° C for 2 h, the precipitated m-chlorobenzoic acid was removed by filtrating under vacuum and this solid was twice washed with 25 ml of cold chloroform and filtered after each washing. The combined chloroform filtrate, containing the product,

was washed with 100 ml of saturated aqueous sodium carbonate. The aqueous washing was extracted once with 100 ml chloroform and the combined chloroform extracts and filtrate were dried (Na_2SO_4), filtered and freed from solvent in a rotary evaporator under reduced pressure. The clear, colorless residual liquid was then fractionally distilled affording 20 g (76%) of product. B. p., 56° at 2 mm; n_D^{23}, 1.4548. Anal. calcd. for $C_6H_{12}O_3$: C, 54.52; H, 9.16. Found: C, 54.58; H, 9.18. Lit. value for probably a cis, trans mixture, b.p., 42-45° at 0.9 MM; n_D^{22}, 1.4553 (26).

3,5-Dinitrobenzoate of trans-3-hydroxy-2-Methoxytetrahydropyran

To 660 mg (0.005 mole) of 3-hydroxy-2-methoxytetrahydropyran in 5 ml of dry pyridine was added 1.38 g (0.006 mole) of 3,5-dinitrobenzoyl chloride. The resultant solution was heated on a steam bath for 25 min. cooled to room temperature and the pyridine removed under reduced pressure on the rotary evaporator. The residue was taken up in 50 ml of chloroform (Diisopropyl ether was also used as a solvent but due to its hazardous property of formation of explosive peroxides while in storage its use was discontinued early in this work.) The chloroform solution was washed successively with 10 ml of water, 15 ml of

15% of aqueous sodium carbonate solution and then 10 ml of water. The dried (Na_2SO_4) chloroform solution was filtered and then freed of solvent on the rotary evaporator. The amber colored residue was taken up in 100 ml of methanol. To this was added 50-60 mg of decolorizing charcoal and the mixture heated to boiling on a steam bath. The hot mixture was filtered to give a clear colorless solution. To this cooled solution was added water until it became cloudy. The mixture was heated to boiling, then placed in the refrigerator overnight. The colorless crystals were separated by filtration under vacuum washed with water and twice recrystallized from methanol-water. The solid so obtained was dried in a vacuum dessicator (0.5 mm) at room temperature giving 1.2 g of the pure derivative. M.p., 133°, Anal. calcd. for $C_{13}H_{14}N_2O_8$: C, 47.86; H, 4.33; N, 8.59. Found: C, 48.21; H, 4.49; N, 8.42.

The following compounds were prepared according to the procedure described above for the preparation of trans-3-hydroxy-2-methoxytetrahydropyran. Their 3,5-dinitrobenzoate derivatives were also prepared as detailed above.

Trans-2-ethoxy-3-hydroxytetrahydropyran from 3,4-dihydro-2H-pyran and ethyl alcohol. Yield, 70%. B.p., 63° at 2.5 mm; n_D^{25}, 1.4506. Anal. calcd. for $C_7H_{14}O_3$: C, 57.51; H, 9.65.

Found: C, 57.65; H, 9.65.

3,5-Dinitrobenzoate: M.p., 117°. Anal. calcd. for $C_{14}H_{16}N_2O_8$: C, 49.42; H, 4.74; N, 8.23. Found: C, 49.70; H, 4.77; N, 8.30.

Trans-3-hydroxy-2-isoproproxytetrahydropyran from 3,4-dihydro-2H-pyran and isopropyl alcohol. Yield, 70%. B.p., 64° at 2 mm; n_D^{25}, 1.4467. Anal. calcd. for $C_8H_{16}O_3$: C, 59.97; H, 10.07 Found: C, 59.71; H, 9.93.

3,5-Dinitrobenzoate: M.p., 97°. Anal. calcd. for $C_{15}H_{18}N_2O_8$: C, 50.85; H, 5.12; N, 7.91. Found: C, 51.02; H, 5.02; N, 8.05.

Trans-2-t-butoxy-3-hydroxytetrahydropyran was prepared as above. However due to the fact that t-butyl alcohol solidifies at ~25° a 2:1 mixture (by volume) of the alcohol and anhydrous chloroform was used as solvent. Work-up of the product was the same as above. Yield 80%. B.p. 62° at 1.5 mm; n_D^{25}, 1.4487. Anal. calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.15; H, 10.21.

3,5-Dinitrobenzoate: M.p., 86-88°. Calcd. for $C_{16}H_{20}N_2O_8$: C, 52.17; H, 5.47; N, 7.61. Found: C, 52.13; H, 5.52; N, 7.68.

Isomerization of trans-and cis-2-methoxy-3-hydroxytetrahydropyrans.

A solution of 10.5 g (0.13 mole) of trans-3-hydroxy-2-methoxytetrahydropyran in 100 ml of anhydrous methanol containing

100 mg of p-toluenesulfonic acid, was heated under reflux for 2 h. The progress of isomerization was monitored by g. l. c. analysis of aliquots of the reaction mixture. After the first hour of heating the trans and cis isomers were found to be in the ratio 55:45. After 1. 5 h the ratio was 61:39, which remained unchanged during the next 2 h. The trans to cis ratio of 61:39 was taken as the equilibrium value. The same (61:39) ratio was obtained from the integrated anomeric (H-2) signals of the crude mixture freed of solvent.

Sufficient powdered (commercial) sodium methoxide was added to the reaction mixture to render the solution neutral. The bulk of the solvent was removed in a rotary evaporator and the residue was taken up in 100 ml of ether. The ethereal mixture was washed with water (25 ml), dried (Na_2SO_4) and filtered. The ether was removed by distillation leaving behind a clear colorless oil. The oil was fractionally distilled under reduced pressure to give 9. 65 g (92%) of a mixture of trans-and cis-3-hydroxy-2-methoxy-tetrahydropyrans, shown by g. l. c. analysis to be in the ratio 61:39, respectively.

B. p. 48-50° at 1. 0 mm; n_D^{25}, 1. 4525. Lit. value (for cis, trans isomeric mixture) B. p. 42-45° at 0. 9 mm; n_D^{22}, 1. 4553 (26). The n. m. r. spectrum of cis- and trans-3-hydroxy-2-methoxytetrahydropyran is shown in Fig. 1.

The isomeric mixture was separated by preparative g.l.c. on a column of 20% butanediol succinate on Gas Chrom-P using a column temperature of 175° and helium flow rate of 105 ml per min. Small volumes (150 μl) of the mixture were injected manually and the separated isomers collected semi-automatically (manual activation) with the automatic sample collector on an Aerograph Autoprep chromatograph. Reinjection of each of the separated components showed only one peak for each. This indicates that separation of the mixture was complete and that no decomposition had taken place.

The minor (39%, cis-isomer) component had the following physical characteristics: B.p., 62° at 2.2 mm; n_D^{25}, 1.4517. Anal. calcd. for $C_6H_{12}O_3$: C, 54.52; H, 9.16. Found: C, 54.50; H, 9.04.

3,5-Dinitrobenzoate derivative: M.p., 88°. Anal. calcd. for $C_{13}H_{14}N_2O_8$: C, 47.86; H, 4.33; N, 8.59. Found: C, 47.70; H, 4.23; N, 8.46.

The n.m.r. spectrum for cis-3-hydroxy-2-methoxytetrahydropyran showed a signal for H-1 at τ 5.43 ($J_{2,3}$=3.2 Hz).

A quantity (1.0 g) of cis-3-hydroxy-2-methoxytetrahydropyran was refluxed in 10 ml of methanol, containing 25 mg of

p-toluenesulfonic acid, for 2 h. G.l.c. analysis of the reaction mixture showed the trans and cis isomers to be in the ratio 61:39, respectively.

Methylation of trans-2-alkoxy-3-hydroxytetrahydropyrans.

The alcohols described above were methylated according to the procedure of Diner, et al (61).

Trans-2, 3-dimethoxytetrahydropyran from trans-3-hydroxy-2-methoxytetrahydropyran.

A quantity (10.6 g, 0.13 mole) of the alcohol was added dropwise to a mixture of 100 ml of 1, 2-dimethoxyethane (previously distilled from $LiAlH_4$), 21.3 g (0.15 mole) of methyl iodide and a suspension of 3.6 g (0.15 mole) of sodium hydride all contained in a 300 ml round bottom flask equipped with a magnetic stirrer, an efficient condenser fitted with a drying tube, and an addition funnel. The reaction temperature was maintained at 5 -10° during addition of the alcohol, by cooling with an ice bath as required. Hydrogen was evolved continuously and a white precipitate (NaI) accumulated while the alcohol was being added. The mixture was then stirred for 2 h at room temperature, after which time the bulk of solvent was removed by fractional distillation. This resulted in further deposition of sodium iodide. The residual mixture was shaken

with 100 ml of anhydrous ether, then filtered under vacuum to collet the sodium iodide and unreacted sodium hydride*, the filtrate was washed with 25 ml of water containing 0.25 g of sodium bisulfite. The clear, colorless ether solution was dried (Na_2SO_4), filtered and freed of solvent by fractional distillation. The residual oil was distilled under reduced pressure to give 10.5 g (85% yield) of pure product. B.p., 110-111° at 110 mm; n_D^{25}, 1.4318. Anal. calcd. for $C_7H_{14}O_3$: C, 57.51; H, 9.65; Found: C, 57.40; H, 9.63.

Trans-2-ethoxy-3-methoxytetrahydropyran was obtained from trans-2-ethoxy-3-methoxytetrahydropyran, by the procedure described immediately above. Yield, 81%. B.p., 46-47° at 5.2 mm; n_D^{25}, 1.4322. Anal. calcd. for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 60.00; H, 9.90.

Trans-3-methoxy-2-isopropoxytetrahydropyran was made from trans-3-hydroxy-2-i-propoxytetrahydropyran, by the procedure described above. Yield, 80%. B.p., 92-93° at 30 mm (56-57° at 7 mm); n_D^{25}, 1.4299. Anal. calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 62.26; H, 10.31.

* The sodium hydride was destroyed by cautiously adding it in small portions, to cold ethyl alcohol.

Trans-2-t-butoxy-3-methoxytetrahydropyran was prepared as above from trans-2-t-butoxy-3-hydroxytetrahydropyran. Yield, 86%. B.p., 61-62° at 7 mm; n_D^{25} 1.4322. Anal. calcd. for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.86; H, 10.51.

II. PREPARATION OF CIS AND TRANS-TETRAHYDROPYRANO-[2,3-b]-1,4-DIOXANE.

Cis and trans-2-(β-chloroethoxy)-3-hydroxytetrahydropyran

The procedure of Barker et al was followed (34), using m-chloroperoxybenzoic acid as the oxidizing agent. From 0.2 mole of 3,4-dihydro-2H-pyran there was obtained an oil which was dissolved in water and the whole extracted with ether. The water layer was then freed from water by fractional distillation under vacuum giving 18 g of the crude diol, 2,3-dihydroxytetrahydropyran. The n.m.r. spectrum in D_2O showed a doublet at τ 5.42 ($J_{2,3}$=6.5 Hz) and at τ 4.99 ($J_{2,3}$=2.5 Hz). The signals in $CDCl_3$ were at τ 5.53 (doublet, $J_{2,3}$=6.5 Hz) and at τ 5.05 (doublet, $J_{2,3}$=2.5 Hz). These were due to the anomeric protons of the trans and cis isomers respectively.

The crude diol (18 g) was mixed with 16 g (0.2 mole) of β-chloroethanol (Eastman-Kodak) in 150 ml of benzene. p-Toluenesulfonic acid (100 mg) was added and water was removed by azeotropic distillation using a Dean-Stark apparatus (101). When about 4 ml of water had accumulated (3 h), the mixture was cooled to 20° and a slight excess of powdered anhydrous potassium carbonate was added. The mixture was stirred for 0.5 h and then the benzene was

removed below 40° with a rotary evaporator. An ether solution (200 ml) of the residual oil was shaken with 50 ml of 10% aqueous sodium carbonate then washed with water (25 ml). The ether layer was dried (Na_2CO_3 + Na_2SO_4), filtered, then freed from solvent with a rotary evaporator. The residual colorless liquid was distilled under reduced pressure in a spinning band column. Yield, 14.5 g (53% based on the crude diol) of a mixture of cis- and trans -2-(β-chloroethoxy)-3-hydroxytetrahydropyran. B.p., 96-97° at 2 mm. n_D^{25}, 1.4754. Anal. calcd. for $C_7H_{13}O_3Cl$: C, 46.53; H, 7.25; Cl, 19.65. Found: C, 46.51; H, 7.25; Cl, 19.76.

The infrared spectrum (neat) showed a broad band centered at 3430 cm^{-1} (OH) with a slight shoulder at 3540 cm^{-1}.

The integrated n.m.r. spectrum indicated a ratio of cis to trans, in the initially isolated product, of 69:31. The 60 M Hz n.m.r. spectrum of the cis-trans mixture showed signals for the anomeric proton at τ 5.31 (a doublet, $J_{2,3}$=3.2 Hz) for the cis isomer, and at τ 5.71 (a doublet, $J_{2,3}$=5.0 Hz) for the trans isomer. In dimethyl sulfoxide-d_6 containing D_2O the doublets were found at τ 5.24 and τ 5.57 respectively for the cis and trans isomers.

G.l.c. with a Burrell K-2 Kromotog using a 2.5 metre column

packed with 20% butanediol succinate on Chromosorb B, and a helium flow rate of 65 ml/min, column temperature of 185° , failed to separate the isomers but did show two overlapping peaks in a ratio of 69:31 corresponding to cis and trans isomers respectively. The major component here was assigned as the cis isomer because of the information obtained by n.m.r.

Increase in the column temperature to 205° gave better separation of the peaks. By use of an Aerograph Autoprep, these two isomers were collected. Reinjection of each showed that the material collected was actually a mixture of materials, probably decomposition products along with the major peak of the unchanged isomer.

The 69:31 cis-trans isomeric mixture (500 mg) was dissolved in 5 ml of β -chloroethanol. p-Tolenesulfonic acid (50 mg) was added and the solution, occasionally shaken, was allowed to stand at room temperature for three days. Aliquots were taken at intervals and analyzed by gas liquid chromatography. After the 3-day period of standing, the mixture was heated for 1 hour at 60 °, then cooled, dissolved in 50 ml of methylene chloride and washed with 15 ml of 10% aqueous sodium carbonate and finally with water. The dried solution ($MgSO_4$) was filtered then freed from solvent by rotary evaporator. The

residue was analyzed by g. l. c. and by n. m. r. spectroscopy.. Table II summarizes the results of the equilibration.

Cis and Trans - tetrahydropyrano [2, 3-b] -1, 4-dioxane

A solution of 5.4 g (0.03 mole) of the cis, trans mixture of 2-(β-chloroethoxy)-3-hydroxytetrahydropyran in 50 ml of 1, 2-dimethoxyethane (dried by distillation from $LiAlH_4$) was added drop-wise to a vigorously stirred suspension of 0.96 g (0.04 mole) of sodium hydride in 50 ml of dry 1, 2-dimethoxyethane in a round bottom, 3-neck flask equipped with a thermometer, condenser, drying tube and an addition funnel. The pyran was added over a period of 1 h during which time the temperature of the reaction mixture rose no higher than 35 °, and the grey suspension of sodium hydride was replaced by a white suspension of NaCl. Hydrogen was evolved. The reaction mixture was stirred overnight at room temperature, then reduced to half its volume by removal of solvent through a spinning band fractionating column at atmospheric pressure. The cooled mixture was then diluted with an equal volume of dry ether to assist in precipitation of the NaCl. The precipitate was removed by filtration under vacuum and the clear filtrate was freed of solvent with a spinning band column. The residue was distilled under reduced pressure, giving 2.5 g of a liquid (cis isomer) boiling at 80° at

20 mm, (n_D^{25}, 1.4689), and 1.3 g of material boiling at 65° at 5 mm (trans isomer). The latter distillate solidified spontaneously in the receiver. Total yield of both cis and trans isomers was 88%. The solid trans isomer was readily crystallized from Skellysolve B giving long prisms melting at 64°.

G.l.c. on a column filled with 20% butanediol succinate on Gas Chrom P, as well as n.m.r. analysis showed that these separated isomers were isomerically pure.

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.31: H, 8.39; Found: for cis isomer: C, 58.26; H, 8.20, and for trans isomer: C, 58.62; H, 8.06.

The 100 M Hz spectrum showed for the cis isomer the signal for the anomeric proton (H-1) at τ 5.49 as a doublet, $J_{1,6}$=1.3 Hz (Fig. 2) and for the trans isomer the signal for the anomeric proton at τ 5.84 as a doublet, $J_{1,6}$= 7.1 Hz (Fig. 3).

III. PREPARATION OF CIS- AND TRANS-2,4-DIMETHOXYTETRAHYDROPYRAN.

Cis- and trans-2,4-dimethoxytetrahydropyran

To a stirred solution of 100 mg of p-toluenesulfonic acid in 100 ml of anhydrous methanol was added 11.4 g (0.10 mole) of 2-methoxy-5,6-dihydro-2H-pyran (see page 191 for preparation of this olefin). The mixture warmed spontaneously over the next 5-10 min and was subsequently heated under reflux for 4 h. The cooled solution was neutralized with powdered sodium methoxide and the bulk of the solvent then removed by fractional distillation. The residue, dissolved in 100 ml of ether, was washed with 15 ml of water then dried ($MgSO_4$), filtered, and freed from solvent by fractional distillation. The residual oil, distilled under reduced pressure, gave 13.5 g (92%) of material which by g.l.c. and by n.m.r. was shown to be a mixture of two isomeric components in the ratio 4.0:1.0. B.p. of the mixture, 109° at 100 mm; n_D^{25}, 1.4330. Anal. calcd. for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.44; H, 9.33.

The two isomers were separated by gas liquid chromatography with a Model A700 Aerograph Autoprep equipped with a 1/4" (O.D.) x 12' stainless steel column packed with 20% butanediol

succinate on Gas-Chrom P. Helium was the carrier gas at a flow rate of 110 ml/min. The column temperature was 160° and 175 μl quantities were injected manually. Retention times for the major and minor constituents were 190 sec and 260 sec respectively. Reinjection of these collected fractions showed that they consisted of only one component each and had suffered no decomposition.

Major component (trans isomer), n_D^{25}, 1.4324. Anal. calcd. for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.54; H, 9.47. Minor component (cis isomer), n_D^{25}, 1.4370. Anal. Found: C, 57.06; H, 9.30.

The n.m.r. spectra are shown in Figs. 4-6. Cis, trans mixture, Fig. 4. Trans isomer Fig. 5; H-2 (anomeric), triplet centered at τ 5.28, $J_{2,3}$, $=J_{2,3}=2.9$ Hz. Cis isomer Fig. 6; H-2 (anomeric), quartet centered at τ 5.68 , $J_{2,3}=8.3$ Hz., $J_{2,3}=2.8$ Hz. All couplings are the observed values.

Equilibration of cis- and trans-2,4-dimethoxytetrahydropyrans.

To separate solutions of 50 mg of each isomer in 5 ml of dry methanol was added 5 mg of p-toluenesulfonic acid. The solution was stirred at room temperature (25°) for several days. At regular intervals aliquots were removed from each solution and

analyzed by gas liquid chromatography using the system described above. Equilibrium was attained within 7 days and in both cases the 4.0:1.0 ratio of trans and cis isomers was obtained.

Cis- and trans-4-hydroxy-2-methoxytetrahydropyran

A mixture of 2 g of Amberlite IR-120 and 10 g (0.087 mole) of 2-methoxy5,6-dihydro-2H-pyran in 100 ml of water was stirred for 3 h at room temperature. The resin was removed by filtration and washed with water (4 x 10 ml). The combined filtrate and washings were freed from water on a rotary evaporator under vacuum at 45°. The residue was shaken with 50 ml of dry benzene and the solution freed of solvent in a rotary evaporator under vacuum thus removing the last of the water by azeotropic distillation. The syrupy residue was taken up in 100 ml of dry methyl alcohol and to this was added 10 g of anhydrous $MgSO_4$ and 100 mg of p-toluenesulfonic acid. This mixture was stirred at room temperature for 48 h, then neutralized with powdered sodium methoxide and filtered. The filtrate was freed from solvent in a rotary evaporator under vacuum. The oily residue was dissolved in 50 ml of ether, washed with 10 ml of water and dried ($MgSO_4$). The ether solution was filtered and freed from solvent to give 2.5 g of a crude oil. G.l.c. analysis of this oil was done

with the apparatus described above. The column temperature in this case was 180°. Five components were obtained. In order of increasing retention time the first three were found, by comparison with authentic samples, to be respectively 2-methoxy-5,6-dihydro-2H-pyran, trans- and cis-2,4-dimethoxytetrahydropyran. The final two components to emerge were found to be trans- and cis-4-hydroxy-2-methoxytetrahydropyran. These last two components were collected as a mixture by preparative g.l.c. using the Aerograph as described above. B.p. (micro), 56-58° at 3 mm; n_D^{25}, 1.4560. Anal. calcd. for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.63; H, 9.24.

G.l.c. analysis of a mixture of the above cis- and trans-4-hydroxy-2-methoxytetrahydropyrans and cis- and trans-3-hydroxy-2-methoxytetrahydropyrans (p. 168) showed four peaks. The retention times of the first two peaks were identical with those for the cis- and trans-3-hydroxy-2-methoxytetrahydropyrans.

The signals due to the anomeric protons in the n.m.r. spectra of the isomeric 3-hydroxy-2-methoxy compounds were found at τ5.44 (doublet) and τ5.75, (doublet).

The signals for the anomeric protons of the cis- and trans-4-hydroxy-2-methoxytetrahydropyran appeared as two sets of

overlapping multiplets in the region τ 5.10 - 5.35.

Methylation of the isomeric mixture of cis- and trans-4-hydroxy-2-methoxytetrahydropyran was accomplished by the general procedure described previously (p.171). To 100 mg of the cis-trans mixture in 2 5 ml of dry ether at room temperature was added 3 g of methyl iodide followed by 1 g of sodium hydride. Stirring was continued for 1 h at room temperature. The mixture was filtered under vacuum and the solvent removed from the filtrate. The oily residue (85 mg) was analyzed by g.l.c. No starting material was observed. Only two components were present in the product. These were found to be identical in retention times to the cis- and trans-2,4-dimethoxytetrahydropyrans prepared above.

Attempted equilibration of 2-methoxy-5,6-dihydro-2H-pyran

A solution of 2.24 g (0.01 mole) of 2-methoxy-5,6-dihydro-2H-pyran in 50 ml of dry ether to which was added 10 drops of freshly distilled borontrifluoride etherate, was heated under reflux for 24 h. The solution was cooled and shaken with 2 g of commercial sodium methoxide in 25 ml of dry ether. The resulting mixture was washed successively with 20 ml of 5% aqueous sodium chloride. The ether solution was dried (Na_2SO_4), filtered, and freed from solvent by careful fractional distillation.

The residual oil was distilled under vacuum to give 1.05 g (47%) of starting material (b. p. 65-66° at 65 mm) and a yellow viscous residue (1.1 g) which could not be distilled. The infrared spectrum of the recovered starting material showed no absorption in the region of 1650 cm^{-1} indicative of the presence of an α, β unsaturated ether such as 4-methoxy-1,2-dihydro-4H-pyran (88, 89).

The polymeric substance analyzed for C, 63.83; H, 8.93. Calcd. for $(C_6H_{10}O_2)_n$: C, 63.14; H, 8.83. Molecular weight, by the osmometric procedure using acetone as solvent, was found to be 241 indicative of a dimeric species.

IV. PREPARATION OF 2-ALKOXY-3-HYDROXY-6-METHOXY-METHYLTETRAHYDROPYRANS.

2-Methoxymethyl-3,4-dihydro-2H-pyran

A solution of 2-hydroxymethyl-3,4-dihydro-2H-pyran* (68.4 g, 0.6 mole) and methyl iodide (99.5 g, 0.7 mole) in 350 ml of 1,2-dimethoxyethane (dried by distillation from $LiAlH_4$) was placed in a 1ℓ3-neck flask equipped with an efficient condenser (drying tube), and thermometer and a magnetic stirrer. Then 15.6 g (0.65 mole) of sodium hydride* was added in small portions over a 30 min. period to the cooled (5-10°) mixture. Vigorous hydrogen evolution took place after addition of each of the small portions of the hydride and a white precipitate of sodium iodide accumulated. After all of the hydride had been added, a further quantity (10 ml of methyl iodide was added and the reaction mixture was then stirred at room temperature for 2 h. The volume of the mixture was reduced to one-quarter. Anhydrous ether (100 ml) was added and more sodium iodide precipitated.

* Kindly donated by J. A Craig, Shell of Canada Ltd., Winnipeg, Manitoba

* The sodium hydride (Metal Hydrides Corporation) was a 56% suspension in mineral oil The oil was washed out with anhydrous ether and the hydride obtained by filtration (under vacuum) of small portions thus treated.

The mixture was filtered by suction, the sodium iodide was washed with 25 ml of ether, and the combined washings, and filtrate were freed of the bulk of the solvent by fractional distillation under atmospheric pressure. The residual 1,2-dimethoxyethane was removed by fractional distillation at 100 mm. Further distillation gave 70 g (91%) of the product. B.p., 83-84° at 65 mm; n_D^{27}, 1.4400. Anal. calcd. for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.41; H, 9.30.

3-Hydroxy-2-methoxy-6-methoxymethyltetrahydropyran.

A quantity (13.2 g, 0.11 mole) of 2-methoxymethyl-3,4-dihydro-2H-pyran in 250 ml of dry methanol was cooled to -10° with a dry ice-acetone bath. To this was added a suspension of 19.5 g (0.12 mole) of 80% m-chloroperoxybenzoic acid in 100 ml of chloroform in small portions at a rate to maintain the reaction temperature in the range -10° - -5°. The work-up was accomplished in the same manner as for trans-3-hydroxy-2-methoxytetrahydropyran (p.165). Fractional distillation of the crude oil gave 11.5 g (62% yield) of a mixture of isomers. B.p., 83-85° at 1.5 mm (125 °); n_D^{24}, 1.4553. Anal. calcd. for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.43; H, 9.15

G.l.c. analysis of the oily product showed two peaks

in the ratio 85:15.

3,5-Dinitrobenzoate derivative of the mixture; M. p. 139-141°

Anal. calcd. for $C_{15}H_{18}O_9N_2$: C, 48.65; H, 4.90; N, 7.57. Found: C, 48.60; H, 5.03; N, 7.29.

The n.m.r. data for the 2-alkoxy-3-hydroxy-6-methoxymethyltetrahydropyrans and 2-alkoxy-3-methoxy-6-methoxymethyltetrahydropyrans are presented in Table IV on page 63.

2,3-Dimethoxy-6-methoxymethyltetrahydropyran.

The alcohol was methylated following the same procedure as used for the methylation of 2-hydroxymethyl-3,4-dihydro-2H-pyran above (p.185). The quantities of material used were 12.8 g (0.1 mole) of 3-hydroxy-2-methoxy-6-methoxymethyltetrahydropyran, 21.3 g (0.13 mole) of methyl iodide, 100 ml of dry dimethoxyethane and 2.64 g (0.11 mole) of sodium hydride. There was obtained by distillation 11.97 g (85%) of pure product. B.p., 43° at 0.25 mm; n_D^{24}, 1.4394. Anal. calcd. for $C_9H_{18}O_4$: C, 56.82; H, 9.54; Found: C, 56.73; H, 9.44.

2-t-Butoxy-3-hydroxy-6-methoxymethyltetrahydropyran.

To 12.8 g (0.1 mole) of 2-methoxymethyl-3,4-dihydro-2H-pyran in a mixture of 75 ml of t-butyl alcohol and 150 ml of anhydrous ether, stirred and kept between -15° and -10° with a dry

ice-acetone bath, was added in approximately 2 to 3 g portions, a total of 22 g (0.1 mole) of 80% m -chloroperoxybenzoic acid. After addition of oxidant was completed the stirred mixture was allowed to come to room temperature. Stirring was continued overnight (15 h). The bulk of solvent was then removed under reduced pressure with a rotary evaporator at ca. 25°. The residual mixture was taken up in 100 ml of chloroform and the solution cooled at about -10° for 4 h to precipitate m -chlorobenzoic acid. The mixture was filtered under vacuum and the solid was washed thrice with 25 ml portions of cold chloroform. The combined chloroform washings and filtrate were extracted with 35 ml of saturated aqueous sodium carbonate then washed with 25 ml of saturated aqueous sodium chloride. The chloroform solution was dried (Na_2SO_4), filtered and freed of solvent in a rotary evaporator at 35° . The residual clear, colorless oil was distilled under reduced pressure to give 9.5 g (44%) of a pure oily product. B.p. 75° at 0.25 mm; n_D^{25}, 1.4504. Anal. calcd. for $C_{11}H_{22}O_4$: C, 60.52; H, 10.16. Found: C, 60.18; H, 9.94.

V. PREPARATION AND $LiAlH_4$ REDUCTION OF 2-ALKOXY-3,4-EPOXYTETRAHYDROPYRANS.

Trans-3-bromo-2-methoxytetrahydropyran

A modification of the published procedure (37, 56) permitted a greater stereoselectivity than that previously obtained (37, 56). The whole synthesis was done in an efficient fume hood.

A solution of 3,4-dihydro-2-H-pyran (84 g, 1 mole) in a mixture of 100 ml of anhydrous liquid ammonia and 1 l of methanol was cooled to -60° with a dry ice-acetone bath. To the stirred solution, kept between -60° and -55°, was added dropwise, over a 2 h period, a solution of 160 g of bromine in 200 ml of carbon tetrachloride. A precipitate of ammonium bromide appeared when half of the bromine had been added. When the bromine addition was completed the cooling bath was removed and the reaction mixture was stirred overnight and thus came to room temperature. The residual ammonia and methanol were removed in a rotary evaporator (bath temperature 50°) under reduced pressure attained by a water pump. To the remaining material was added 500 ml of dry ether. The precipitated ammonium bromide was removed by filtration at reduced pressure, the solid subsequently washed with water (2 x 100 ml). The ether layer was dried (Na_2SO_4) and freed

from solvent by rotary evaporator. The residue was distilled under reduced pressure and afforded 165 g (85%) of trans-3-bromo-2-methoxytetrahydropyran whose integrated 100 M Hz. n.m.r. spectrum agreed with the structure and showed evidence (at high amplitude) for only a small amount (<5%) of the cis isomer. G.l.c. showed the cis isomer to be present in 1%.

The use of 2 moles of sodium methoxide rather than ammonia in the above reaction gave equally good results. B.p. 87° at 12 mm; n_D^{25}, 1.4843. Lit. (a) B.p. 88-89° at 18 mm; n_D^{25}, 1.4838 (56)*.

*Probably for a mixture of cis and trans isomers.

(b) B.p. 78° at 10 mm; n_D^{25}, 1.4841 (3;7)**.

** For a 2:3 mixture of cis and trans isomers.

100 M Hz n.m.r. data for the cis and trans isomers:

	H-2	$J_{2,3'}$ Hz	Ref.
Trans	5.50 (doublet)	3.9	This work
	5.54 (doublet)	3.9	(37)
Cis	5.42 (doublet)	2.8	This work
	5.45 (doublet)	2.7	(37)

The preparation of trans-3-bromo-2-t-butoxytetrahydropyran followed the same procedure as above. However, in this case a 40% solution of t-butyl alcohol in ether, rather than pure t-butyl alcohol, was used as solvent to avoid solidification of the alcohol when the mixture was cooled and diluted with liquid ammonia. Yield, 80%. B.p. 75° at 1.5 mm; n_D^{25}, 1.4726. Anal. calcd. for $C_9H_{17}BrO_2$: C, 45.58; H, 7.23; Br, 33.70. Found: C, 45.64; H, 7.05; Br, 33.85. The 60 M Hz n.m.r. spectrum showed a signal for H-2 at τ 5.27 (doublet), $J_{2,3}$=5.5 Hz.

2-Methoxy-5,6-dihydro-2H-pyran from trans-3-bromo-2-methoxytetrahydropyran. Dehydrobromination of the bromide to give the olefin was accomplished by a modification of a procedure by Woods and Sanders (56). A quantity(58 g, 0.4 mole) of trans-3-bromo-2-methoxytetrahydropyran in a solution of 81 g (1.5 mole) of sodium methoxide in 500 ml of methanol was heated under reflux for 24 h. The volume of the reaction mixture was reduced to one-half by fractional distillation using a 60 mm Vigreux column. An equal volume (250 ml) of ether was added to the cooled mixture. The insoluble salt was removed by filtration under vacuum and washed with ether (2 x 25 ml). The combined washings and filtrate were washed with water (2 x 50 ml), dried (Na_2SO_4), filtered and freed

of solvent by fractional distillation. The amber colored oily residue was distilled to give 32 g (70%) of the pure olefin. B. p. 134° at 705 mm; n_D^{25}, 1.4420. Lit. b.p., 136-138°; n_D^{25}, 1.4425 (56).

The 60 M Hz n.m.r. spectrum of the olefin showed for the anomeric (H-2) proton a broad singlet at τ 5.30 (W/2=5 Hz).

Note: This trans-3-bromo-2-t-butoxytetrahydropyran could be distilled successfully only under vacuum and at a pressure which required the heating bath temperature to be no higher than 95°. Higher bath temperatures caused violent decomposition of the distilling liquid.

2-Methoxy-5,6-dihydro-2H-pyran

2-t-Butoxy-5,6-dihydro-2H-pyran was prepared by a procedure similar to that employed for the methyl homologue above but modified as follows.

Sodium hydride (Metal Hydrides Corp.) was added slowly to dry t-butyl alcohol (kept between 30° and 40°) to form sodium t-butoxide. To a solution of 3 molar equivalents of sodium t- butoxide in t-butyl alcohol (about 8 times the weight of the bromo compound) was added, gradually, one molar equivalent of 3-bromo-2-t-butoxytetrahydropyran (neat). The solution temperature rose to 60°. When the initial exothermic reaction had subsided, the solution was heated underreflux overnight, then reduced to half

its volume by fractional distillation at atmospheric pressure. To the residue was added an equal volume of dry ether to complete the precipitation of the sodium bromide. The solid, removed by filtration under suction, was washed once with ether. The combined ethereal washings and filtrate were washed once with water and dried (Na_2SO_4). After separation of the solid, the solvents were removed by fractional distillation at atmospheric pressure and then the residual oil was distilled under vacuum, giving pure 2-t-butoxy-5,6-dihydro-2H-pyran. G.l.c. showed the presence of only one component. Yield, 70%: B.p., 80° at 45 mm, and 103° at 100 mm; n_D^{25}, 1.4397. Anal. calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.99; H, 9.90. The 60 M Hz n.m.r. spectrum showed a broad singlet (envelope) for H-2 centered at τ 4.88 (W/2=5Hz).

3,4-Epoxy-2-methoxytetrahydropyran (XXXVII, a and b).

To 27 g (0.24 mole) of 2-methoxy-5,6-dihydro-2H-pyran in 275 ml of dry ether contained in a 500 ml, 3-neck flask equipped with a magnetic stirrer, condenser (with drying tube) and thermometer, was added 60 g (0.27 mole) of 80% m-chloroperoxybenzoic acid. Cautious addition of the oxidizing agent was found to be unnecessary since epoxidation in this system occurs very slowly. The peroxy acid dissolved readily. The mixture was

stirred at ~35° for several days. G.l.c. of an aliquot showed that little reaction had occurred in the first 24 h. In 2.5 days a precipitate of the slightly soluble m-chlorobenzoic acid appeared and accumulated with time. After seven days of reaction the mixture was cooled in a refrigerator for 2 h, then filtered by suction. The solid m-chlorobenzoic acid was washed with cold ether. The combined ether solutions from the washings and filtrate were extracted with saturated aqueous sodium carbonate (3 x 25 ml) and the sodium carbonate solutions in turn extracted with ether. The combined ether solutions were dried (Na_2SO_4) and filtered. Removal of the ether by fractional distillation at atmospheric pressure left an oil which was distilled under vacuum giving 25 g (80%; a second run gave 85%) of 3,4-epoxy-2-methoxytetrahydropyran. N.m.r. and g.l.c. analysis showed this to be a mixture of cis and trans isomers in the ratio of 25:75. These were separated by g.l.c. using an Aerograph Autoprep, Model A-700 with a 20' x 1/4" (ID) column packed with 25% Carbowax 20 M on Gas-Chrom P (60-80 mesh) and helium as the carrier gas at a flow rate of 110 ml/min. Column, injector and detector temperatures were 175°, 190° and 190° respectively. For the trans:cis mixture (XXXVIIa:XXXVIIb=75:25): B.p. 86-88° at 100 mm; n_D^{25} 1.4445. Anal. calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.74: Found: C, 55.04; H, 7.52. The n.m.r. spectrum is shown in Fig. 7. The pure

trans isomer (XXXVIIa) boiled at 88° at 100 mm n_D^{25}, 1.4450. Found: C, 55.28; H, 8.00. The n.m.r. spectrum of the trans isomer is shown in Fig. 8. The pure cis isomer (XXXVIIb) boiled at 84° at 100 mm; n_D^{25}, 1.4415. Anal. Found: C, 55.65; H, 7.59. The n.m.r. spectrum of the cis isomer is shown in Fig. 9

2-t-Butoxy-3,4-epoxytetrahydropyran (XXXVII) was prepared in the same manner as described immediately above, starting with 2-t-butoxy-5,6-dihydro-2H-pyran. According to the n.m.r. and g.l.c. analysis, the product was a mixture of cis and trans isomers in the ratio cis/trans = 10%/ 90%. The trans isomer was separated by preparative g.l.c. (via an Aerograph 700; Carbowax 20M column at 170 °; helium flow, 60 ml/min) under the same conditions as for the 2-methoxy homologue. The separation of the cis isomer was abandoned due to its presence in <10% concentration and the partial overlapping of the peaks for the cis and trans isomers. Yield of the cis, trans mixture (1:9) was 82%. B.p. 72-74° at 4.0 mm; n_D^{25}, 1.4475. Anal. calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.35; H, 8.94. The pure trans isomer boiled at 65° at 2.75 mm; n_D^{25}, 1.4480. Anal. Found: C, 63.16; H, 8.87. The 60 M Hz n.m.r. spectrum of the trans, cis epoxide mixture (9:1) showed signals for the H-2 protons at τ 4.90 (singlet, $J_{2,3} \sim 0$) and at τ 4.82 (doublet, $J_{2,3} \sim$ 3Hz), respectively (see Fig. 10).

$LiAlH_4$ Reduction of

(a) 3,4-epoxy-2-methoxytetrahydropyran

A solution of trans-3,4-epoxy-2-methoxytetrahydropyran (80 mg, 6×10^{-4} mole) in 20 ml of dry ether was added slowly and dropwise to a stirred solution of $LiAlH_4$ (0.03 g, 8×10^{-4} mole) in 25 ml of dry ether at room temperature. Each drop caused a vigorous reaction. After the addition was complete, the reaction mixture was stirred and left over-night at room temperature. The aluminum complex was then decomposed by gradual addition of 15 ml of ether saturated with water, followed by 1 ml of 15% aqueous sodium hydroxide. The granular precipitate was filtered by gravity and the colorless solid washed with ether (5 x 10 ml). The combined ether solution from the washings and filtrate were dried (Na_2SO_4) and freed from solvent at room temperature under vacuum (20 mm) using a rotary evaporator. Analysis of the residual colorless oil by g.l.c. on a 1/4" x 20' column of 20% butanediol succinate on Chromosorb-P (60-80 mesh) showed that it consisted of one major product to the extent of 95%. No evidence was obtained for the cis isomer or other isomeric products. The contaminant present proved to be diethyl ether. The n.m.r. and i.r. spectra of the oil were identical in all respects

with those obtained from authentic trans-3-hydroxy-2-methoxy-tetrahydropyran. The retention time on the gas liquid chromatogram was identical to that of an authentic sample of trans-3-hydroxy-2-methoxytetrahydropyran (page 165).

A solution of cis-3,4-epoxy-2-methoxytetrahydropyran (120 mg, 9×10^{-4} mole) in 5 ml of anhydrous ether was added to 0.45 g of lithium aluminum hydride in 35 ml of ether. The mixture was stirred overnight at room temperature, then diluted with 20 ml of ether, and cooled to 0°. The complex was destroyed by cautious addition of 1 ml of water, then 1 ml of 15% aqueous sodium hydroxide followed filtered. The granular residue was washed with ether (3 x 15 ml). The combined ether solutions were dried (Na_2SO_4) and freed from solvent at atmospheric pressure. The residual oil (110 mg, 83%) contained only one component when analyzed by g.l.c. on an F and M Model 700 Laboratory Chromatograph using 20' x1/4" column packed with 20% butanediol/succinate on Gas Chrom P (60-80 mesh) at 175°, and helium flow rate of 100 ml/min. This had a retention time and an n.m.r. spectrum identical to those for authentic cis-3-hydroxy-2-methoxytetrahydropyran. The 3,5-dinitrobenzoate of this oil melted at 87-88° (crystallized from methyl alcohol-water) and was identical (nuclear magnetic resonance

spectrum) with the 3,5-dinitrobenzoate of authentic cis-3-hydroxy-2-methoxytetrahydropyran (page 170).

(b) Cis-trans-2-t-butoxy-3,4-epoxytetrahydropyran

The 9:1 isomeric mixture (1.72 g, 0.01 mole) of cis-trans-2-t-butoxy-3,4-epoxytetrahydropyran in dry ether (25 ml) was slowly added over a 5 min period to a mixture of 500 mg of lithium aluminum hydride in 35 ml of anhydrous ether. The reaction flask (250 ml) was equipped with a magnetic stirrer, thermometer and condenser with a drying tube. The mixture was stirred at 30-35° overnight (heated only by the stirring motor) and then diluted with 25 ml of ether and cooled with an acetone-dry ice bath kept between -10° and -5°. To the reaction mixture (at ~0°) was added, carefully, 1 ml of water, then 1 ml of 15% aqueous sodium hydroxide and finally 1 ml of water. The contents of the flask were stirred for 30 min to complete the formation of a granular precipitate. The supernatant ether was decanted and the residue extracted successively with ether (3 x 20 ml) and chloroform (1 x 20 ml). The combined organic extracts were dried with anhydrous sodium sulfate containing a small amount of dry sodium carbonate to prevent any acid catalyzed isomerizations. After separation of the solid, the filtrate was freed from solvent at atmospheric

pressure. Residual solvent was removed under reduced pressure with a rotary evaporator. In the last two steps some dry sodium carbonate was added to prevent acid catalyzed isomerization. Analysis of the residual oil (1.65 g, 86%, after subtraction of 5% of remaining solvent)by g.l.c. (F and M Chromatograph, Model 700; 20' x 1/4" column of 20% Carbowax 20 M on Gas Chrom P, 60-80 mesh; column temperature, 175°; helium flow, 60 ml/min) showed the presence of only two compounds in the ratio 9:1, plus 5% of solvent. The retention times of these two compounds (ratio 9:1) were identical to those of authentic trans-2-t-butoxy-3-hydroxytetrahydropyran and its 2-3% contaminant of cis-2-t-butoxy-3-hydroxytetrahydropyran.

A n.m.r. spectrum of the residual oil above showed, by integration of the signals for the anomeric protons, a ratio of trans to cis isomers of about 9:1. This spectrum was superimposable on that of authentic trans-2-t-butoxy-3-hydroxytetrahydropyran containing 2-3% of the cis-isomer (page 168).

VI. PREPARATION, AND TREATMENT WITH ETHANOLIC SODIUM ETHOXIDE, OF THE ISOMERIC 3,4-DIBROMO-2-ETHOXYTETRAHYDROPYRANS.

Trans-3-bromo-2-ethoxytetrahydropyran was prepared according to the procedure used for trans-3-bromo-2-methoxytetrahydropyran (p.189)using ethanol as the solvent. From 84 g (1.0 mole) of 3,4-dihydro-2H-pyran in 1 l of ethanol there was obtained 185 g (89%) of 3-bromo-2-ethoxytetrahydropyran which, according to g.l.c. and n.m.r. spectrum was the trans isomer to the extent of 98%. B.p., 95-96° at 20 mm, n_D^{25}, 1.4749. Lit. b.p. 94-96° at 18 mm, n_D^{25}, 1.4752 (56).

2-Ethoxy-5,6-dihydro-2H-pyran, was prepared by the following modification of the procedure used for 2-methoxy-5,6-dihydro-2H-pyran (p.191).

A quantity (104 g, 0.5 mole) of trans-3-bromo-2-ethoxytetrahydropyran was added to a stirred solution of 112 g (2 moles) of potassium hydroxide in 600 ml of 95% ethanol. The mixture was heated under reflux for 24 h. The reflux condenser was then replaced by a Vigreux fractionating column and the volume of the reaction mixture reduced to 300 ml by distillation. The amber colored residue, containing precipitated potassium

bromide, was cooled to room temperature and diluted with 500 ml of ether to promote further precipitation of the salt. The mixture was washed with water (4 x 75 ml), then with 50 ml of saturated aqueous sodium chloride and then dried (Na_2SO_4). The filtered liquid was freed fromsolvent by fractional distillation and the residue fractionally distilled under vacuum. Yield, 44.6 g of 2-ethoxy-5,6-dihydro-2H-pyran boiling at 75-76° at 65 mm, or at 150-151° at 705 mm. n_D^{25}, 1.4469. Lit. b.p., 153-155° n_D^{25}, 1.4475 (56). There was recovered 15.5 g of starting meterial, b.p., 95° at 20 mm. Yield, based on material consumed, 76%.

3,4-Dibromo-2-ethoxytetrahydropyran, (XLII, a and b) The following modification of the method of Woods and Temin (75) gave improved results. To a stirred solution of 38.4 g (0.3 mole) of 2-ethoxy-5,6-dihydro-2H-pyran in 150 ml of methylene chloride, cooled to -35° in a dry ice-acetone bath, was added a solution of 48 g (0.3 mole) of bromine in 50 ml of cold methylene chloride at such a rate that the temperature of the reaction mixture remained between -35° and -30°. When all of the bromine had been added, the mixture was stirred for 1 h while it came to room temperature. It was then washed with a solution of 10 g of sodium carbonate and 10 g of sodium bisulfite in 40 ml of water, then with water. The organic layer was separated, dried (Na_2SO_4), filtered and freed

from solvent in a rotary evaporator. The crude product (78 g, 90%) was shown, by its nuclear magnetic resonance spectrum, to contain two isomers in the ratio of 3:1. Distillation of the crude material gave 72 g (83%) of the mixture of isomeric dibromides (XLIIa and XLIIb). B.p., 89-91° at 1.25 mm, n_D^{23}, 1.5217 (Calc d. for n_D^{32}, 1.5181 [107]. Lit. b.p., 80-85° at 0.3 mm, n_D^{32}, 1.5140 (75).

The isomers were separated by dissolving 42 g of the isomeric mixture in 100 ml of a 1:1 solution of pentane and dry diethyl ether. The solution, when cooled for 1-2 h in a dry ice-acetone bath, deposited 10 g of colorless crystals. Recrystallization of this solid from the same mixed solvent gave 9.8 g of isomerically pure material (XLIIb). M.p., 58°. Lit. m.p. 60-61 (75). Removal of the solvent from the mother liquor by rotary evaporator gave an oil which was distilled to give 30 g of pure liquid isomer (XLIIa). B.p., 85-86° at 1.5 mm, n_D^{23}, 1.5158. Lit. B.p. 123° at 12 mm, n_D^{25}, 1.5158 (75).

The n.m.r. spectrum (Fig. 13) of the solid isomer showed that it was the all trans XLIIb with substituents preferably in the equatorial arrangement. (see Results and Discussion, Chapter V). The n.m.r. spectrum (Fig. 14) of the liquid isomer (the major component) supported the structural assignment and

preferred conformation as shown in XLIIa(Chart 43, p. 159).

Attempted equilibration of XLIIa and XLIIb

A solution of 250 mg of the liquid 3,4-dibromo-2-ethoxytetrahydropyran, XLIIa , in 10 ml of absolute ethanol containing 100 mg of p-toluenesulfonic acid catalyst, and a similar solution of 250 mg of the solid isomeric 3,4-dibromo-2-ethoxy-tetrahydropyran, XLIIb, were each stirred at room temperature for 24 h. To each was then added sufficient ethanolic potassium hydroxide to neutralize the acid catalyst. The solvent was removed in a rotary evaporator under vacuum and the residual material, in each case, was shaken vigorously with 25 ml of anhydrous ether. The precipitated salt was removed by suction filtration and the filtrate was then freed from ether under reduced pressure with a rotary evaporator. The residues were dissolved in $CDCl_3$ and a n.m.r. spectrum obtained. In either case the only observable signals in the anomeric proton region were those due to the anomeric proton of the unchanged material.

When similar solutions of both the isomers, XLIIa and XLIIb were separately heated under reflux for 12 h, cooled, and then worked up as above, and the resulting materials analyzed by n.m.r. as before, clear evidence of a small amount of isomerization was perceived. The liquid isomer, had isomerized to the

extent of only ~5%, while the solid isomer had isomerized to the extent of only ~10%.

Trans-2, 3-diethoxytetrahydropyran. A modification of the alkylation procedure described on page 171 was employed.

Ethyl iodide (3.9 g, 0.025 mole) was added to a suspension of 0.62 g (0.026 mole) of sodium hydride (Metal Hydrides Corporation) in 125 ml of dry 1, 2-dimethoxyethane, previously distilled from lithium aluminum hydride. To this was added slowly, by means of an addition funnel, a solution of 3.35 g (0.023 mole) of trans-2-ethoxy-3-hydroxytetrahydropyran (p.167) in 24 ml of dry 1, 2-dimethoxyethane. The addition was such that the reaction mixture was maintained at 35°. The mixture was then stirred at room temperature overnight. The solution was worked up according to directions on p. 171. The product (3.40 g, 85%) boiled at 86° at 16 mm, n_D^{23}, 1.4320.

Anal. Calcd. for $C_9H_{18}O_3$, 62.04; H, 10.41. Found: C, 61.96; H, 10.11.

The 60 M Hz n. m. r. spectrum of this compound shows a signal for H-2 at τ 5.55 (doublet, $J_{2,3}$=4.5 Hz).

Isomerization of trans-2, 3-diethoxytetrahydropyran was done by a modification of the directions given for the isomerization of

the analogous trans-3-hydroxy-2-methoxytetrahydropyran (p. 168).

To 1.5 g of trans -2,3-diethoxytetrahydropyran in 25 ml of absolute ethanol was added 100 mg of p-toluenesulfonic acid. The mixture was refluxed for 4 h, then sufficient 10% ethanolic potassium hydroxide was added to the cooled reaction mixture to neutralize the acid. The bulk of the solvent was removed by fractional distillation.

Analysis of the crude mixture by g.l.c. showed two slightly overlapping peaks in the ratio 68% trans:32% cis indicating that isomerization had occurred. The analysis was performed with an F and M Model 700 chromatograph using a column (1/8" x 12') filled with 20% butanediol succinate on Gas-Chrom P (60-80 mesh) at a temperature of 125°. Helium was the carrier gas at a flow rate of 40 ml/min.

The n.m.r. spectrum of this isomeric mixture, showed the two anomeric (H-2) proton signals as doublets at τ 5.18, $J_{2,3}$=4.5 Hz (trans). The cis:trans ratio here too was 1:2.

This isomeric mixture boiled at 85-87° at 15 mm. n_D^{25}, 1.4318. Anal. calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.77; H, 10.27.

Dehydrohalogenation of the 3,4-dibromo-2-ethoxytetrahydro pyrans XLIIa and XLIIb

The 3:1 isomeric mixture of XLIIa and XLIIb (30 g, 0.104 mole) was added to a solution of 9.3 g (0.404 mole) of sodium in 175 ml of absolute ethanol. A slight exothermic reaction occurred and in a few minutes a precipitate accumulated (NaBr). The mixture was heated under reflux for 24 h during which time it developed a deep amber color and the amount of precipitated salt increased. Sufficient solvent was then removed through a fractionating column, to reduce the volume of liquid to one half. To the cooled mixture was added 150 ml of ether to promote precipitation of the salt, and then the whole was washed with water (3 x 50 ml). The ether solution was shaken with charcoal to remove the color, and then filtered. The yellow filtrate was dried ($MgSO_4$) and freed of solvent by fractional distillation. The residual oil was distilled under reduced pressure giving 10.6 g of a liquid (30% yield with respect to the major component, by g.l.c.) boiling at 68-69° at 20 mm. n_D^{28}, 1.4556. A Beilstein test showed this liquid to contain halogenated material.

G.l.c. analysis was made with an Aerograph Autoprep 700 equipped with a column (1/4" x 20') packed with 25% Carbowax 20 M on Gas Chrom P (60-80 mesh). The column temperature was 170° and the flow rate of the helium carrier gas, 100 ml/min. Two peaks were discerned in the area ratio of 6:1. The major peak

was broad and emerged first. The minor component peak was sharp. These two components were separated by g. l. c. using the above apparatus and column. The major component, on re-injection, produced only the same characteristic broad peak. B. p., 72° at 20 mm, n_D^{25}, 1.4450. Lit. b. p., 98-101° at 17 mm, n_D^{27}, 1.445 (75). Elemental analysis of the major component was correct for a diethoxydihydropyran. Anal. calcd. for $C_9H_{16}O_3$: C, 62.64; H, 9.36. Found: C, 62.77; H, 8.90.

The infrared spectrum (neat) showed no absorption between 1610-1690 cm^{-1} (no vinyl ether), and no absorption for OH.

The minor component could have been 3-bromo-2-ethoxy-5,6-dihydro-2H-pyran. Its refractive index, n_D^{25}, 1.4887, agreed with that reported for this compound, n_D^{21}, 1.4900 (75). This substance was of no immediate interest and was thus not examined further.

Hydrogenation of the major component isolated from the above dehydrohalogenation of the 3:1 mixture of XLIIa and XLIIb.

A modification of the published procedure (75) was employed.

The major component (diethoxy dihydropyran) (1.6 g), isolated by g. l. c. as above, was dissolved in 50 ml of 95% ethyl alcohol. The mixture, after the addition of 500 mg of 5% palladium on charcoal catalyst, was shaken with hydrogen at 40 p. s. i. for 2 h at room temperature. The material was filtered and the bulk

of the solvent removed from the filtrate by fractional distillation. The residue was distilled under vacuum and gave 1.35 g (84%) of an oil boiling at 83-84° at 17 mm. n_D^{26}, 1.4312. Lit. b.p., 93° at 15 mm, n_D^{28}, 1.4315 (75).

The elemental analysis agreed with the structure of this material being a diethoxytetrahydropyran. Anal. calcd. for $C_9H_{18}O_3$: C, 62.04; H, 10.41, Found: C, 61.63; H, 10.38.

The material was further analyzed by g.l.c. using an F and M Model 700 Chromatograph equipped with a column (1/8" x 12') at 125 containing 20% butanediol succinate on Gas-Chrom P (60-80 mesh). The helium flow rate was 40 ml/min. The spectrum showed three components whose peaks were in the area ratio of 8:1:1 (in order of their times of appearance). The major component (80%) had a retention time identical with that of trans-2,3-diethoxytetrahydropyran. The two minor peaks were not for the cis-2,3-diethoxytetrahydropyran. Their identity is unknown but it is believed that they are both isomeric diethoxy-tetrahydropyrans because the elemental analysis of the mixture of which they are a part was that for diethoxytetrahydropyyran.

Hydrogenation of the product obtained from the reaction of sodium ethoxide in ethanol with

(i) the isomeric mixture of the 3,4-dibromo-2-ethoxytetrahydro-pyrans XLIIa and XLIIb.

The 3:1 mixture of XLIIa and XLIIb (15 g, 0.052 mole)

was added to a solution of 6 g of sodium in 100 ml of absolute ethanol. This mixture was heated under reflux for 24 h and then its volume reduced to 50 ml by removal of solvent by means of fractional distillation. The cooled residue, in 100 ml of ether, was washed with water (2 x 25 ml) and dried (Na_2SO_4). The drying agent was removed and the filtrate freed from solvent by fractional distillation. The residue, which according to the findings of Woods and Temins (75) contained a mixture of unreacted dibromide, 3-bromo-2-ethoxy-5,6-dihydro-2H-pyran and a diethoxydihydropyran (XLIV, ?). was taken up in 50 ml of anhydrcus ethanol containing 1.5 g of potassium hydroxide. To this was added 500 mg of 5% palladium on charcoal. The resulting mixture was shaken for 24 h at room temperature with hydrogen at 60 p. s. i. The catalyst was separated by filtration, and the filtrate, diluted with 75 ml of ether, was washed with water (3 x 25 ml), dried (Na_2SO_4) and freed from solvent by fractional distillation. The residue was analyzed by g. l. c. on a column (1/8" x 12') of 20% butanediol succinate on Gas Chrom P (60-80 mesh). The column temperature was 125° and helium flow rate, 40 ml/min. Four peaks (A to D in order of appearance) were obtained in the area ratios of 12:8:1:1. The first peak, A, was identical in retention time with

that of 2-ethoxytetrahydropyran (102). The second peak, B, was identical in retention time with that of authentic trans-2, 3-diethoxy-tetrahydropyran. Peaks C or D were not due to cis-2, 3-diethoxy-tetrahydropyran and are as yet unknown. Peaks B, C and D have the same relative areas and retention times as the three peaks obtained by hydrogenation of the diethoxydihydropyran obtained as the major component of the distilled 6:1 mixture from the de-hydrohalogenation of XLIIa and XLIIb (see above).

(ii) The pure liquid 3, 4-dibromo-2-ethoxytetrahydropyran, XLIIa.

Pure XLIIa (15 g, 0.052 mole) was treated as in experiment (i) immediately above. G.l.c. analyses of the product of hydro-genation showed three peaks A, B and C (in order of appearance) in the area ratios of 13:9:1. Peaks A and B were identified as due to 2-ethoxytetrahydropyran and trans-2, 3-diethoxytetrahydropyran respectively. Peak C was unknown but was coincident with C of experiment (i).

(iii) The pure solid 3, 4-dibromo-2-ethoxytetrahydropyran, XLIIb.

Pure XLIIb (10 g, 0.035 mole) was treated as in experiment (i) above. Analysis, by g.l.c. of the product of hydro-genation showed only two peaks, A and D (in order of appearance) in the area ratio of 14: 9. Peak A was identified as due to 2-ethoxy-tetrahydropyran. Peak D is unknown but identical in retention time with Peak D in experiment (i) above.

VII. PREPARATION OF METHYL 4-DEOXY-3-O-METHYL-DL-THREO-PENTOPYRANOSIDE.

Methyl 4-deoxy-3-O-methyl-α,β-DL-threo-pentopyranoside (L and Ll).

A quantity (9.95 g, 0.076 mole) of the 1:3 mixture of cis- and trans-3,4-epoxy-2-methoxytetrahydropyran (page 193) was dissolved in 100 ml of anhydrous methanol containing 100 mg of p-toluenesulfonic acid. The solution was heated under reflux overnight, then cooled to room temperature and neutralized, by the addition of solid sodium methoxide. The methanol was then removed at 45° under vacuum in a rotary evaporator under the vacuum obtained by a water pump. The residue, in 100 ml of methylene chloride, was washed with 10 ml of saturated aqueous sodium carbonate, then with 10 ml of water. The combined washings were extracted with 25 ml of methylene chloride extract and solution were dried (Na_2SO_4), filtered and then freed from solvent at 45° under vacuum in a rotary evaporator. Distillation of the oily residue afforded 9.8 g (76%) of a colorless, viscous oil. B.p., 63-66° at 0.75 mm; n_D^{23}, 1.4575. Calcd. for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51:61; H, 8.43.

The n. m. r. spectrum in $CDCl_3$ (reference, tetramethylsilane) at 60 M Hz using a Varian Associates A60 spectrometer showed two anomeric proton signals at τ5.79 (doublet, $J_{1,2}$ ~2 Hz) and at τ5.92 (doublet, $J_{1',2'}$ ~7 Hz).

G. l. c. analysis on a 12 foot 1/8" O. D. column of 20% butanediol succinate on Gas Chrom P 60-80 mesh, with helium as the carrier gas at a flow rate of 40 ml/min., column temp. 180°, showed the presence of only two components, clearly resolvable.

The 3,5-dinitrobenzoate, obtained in the usual manner, melted at 131-135° (from methanol-water). Calcd. for $C_{14}H_{16}O_9N_2$: C, 47.19; H, 4.43; N, 7.86. Found: C, 47.09; H, 4.36; N, 8.13.

The n. m. r. spectrum in $CDCl_3$ (reference tetramethylsilane) (obtained with a Varian Associates HR 100 spectrometer) clearly showed the presence of two isomers. Analysis of the spectrum is described in the Results and Discussion section, Chapter VI.

4-Deoxy-3-O-methyl-α,β-DL-threo-pentose

Methyl 4-deoxy-3-O-methyl-α,β-DL-threo-pentopyranoside (2 g) was placed in 125 ml of water containing 3 g of

Amberlite IR 120(H°). The mixture was stirred while being heated on a steam bath to 85° -90°for 20 h. The cooled mixture was filtered (gravity) and the ion-exchange resin washed with 15 ml of water and separated. The combined filtrates were freed from water at 45° in a rotary evaporator under reduced pressure and gave 2 g of a colorless syrup. Attempts to crystallize this from a variety of solvents (ethyl acetate, Skellysolve B, methanol, water) failed.

The n. m. r. spectrum in pyridine (reference, tetramethylsilane; A60 spectrometer) showed the presence of two anomeric proton signals at τ4.45 (doublet, $J_{1,2}$ = 2.0 Hz) and τ5.12 (doublet, $J_{1',2'}$ ~ 7.0 Hz). No starting material was detected.

To 0.4 g of 4-deoxy-3-O-methyl-α,β-DL-threo-pentrose was added to 0.8 g of phenylhydrazine hydrochloride followed by 1.2 g of crystalline sodium acetate and then 8 ml of water. To the cloudy solution was added 1 ml of saturated aqueous sodium bisulfite to prevent air oxidation of the product. The mixture, frequently shaken, was heated in a beaker of boiling water for 40 min. After 7 min of heating, light amber colored oil droplets appeared and accumulated. When the solution was cooled, the oil droplets formed an amorphous solid from which the liquid could be decanted. The solid was crystallized from 25 ml of

ethanol-water (3:1 by volume) and gave yellow needles. Two further crystallizations from the same solvent mixture gave 350 mg of the pure phenylosazone of 4-deoxy -3-O -methyl- α, β-DL-threo-pentose. M. p. 121 (dec). Calcd. for $C_{18}H_{22}O_2N_4$: C, 66.23; N, 6.79; H, 17.17. Found: C, 66.44; H, 6.94; N, 17.38.

Nitric acid oxidation of 4-deoxy-3-O-methyl-DL-threo-pentose

The 4-deoxy-3-O-methyl-DL-xylose (1 g) was added to a solution of 4 ml of concentrated nitric acid in 10 ml of water in a porcelain evaporating dish. The mixture was heated on a steam bath, in an efficient hood, until about 2-3 ml of viscous liquid remained. Cooling failed to induce crystallization. The crude material was transferred with 10 ml of water to a flask. The water was removed by a rotary evaporator under vacuum whereupon a colorless solid appeared. This was taken up in 15 ml of hot ethyl acetate, filtered and stored overnight in a refrigerator. The colorless crystals were separated by filtration under vacuum and again crystallized from 10 ml of ethyl acetate. Yield, 550 mg (55%) of pure O-methyl-DL-tartaric acid. M. p. 196-202° (dec). Calcd. for $C_5H_8O_6$: C, 36.59; H, 4.91. Found: C, 36.48; H, 4.80. Lit. for O-methyl-L-tartaric acid, m. p. 179-182° (90).

The infrared spectrum (KBr pellet) was identical with that supplied by Woo et al (90) (see Figs. 15 and 16).

VIII. PREPARATION OF METHYL 4-DEOXY-6-O-METHYL- α -DL-ARABINO-HEXOPYRANOSIDE.

3-Bromo-2-methoxy-6-methoxymethyltetrahydropyran (LIII + LIV).

To a stirred mixture of 52 g (0.41 mole) of 2-methoxymethyl 3,4-dihydro-2H-pyran (p.185), 500 ml of methyl alcohol and 50 ml of anhydrous ammonia, cooled to -60° in a dry ice-acetone bath, was added 65.6 g (0.41 mole) of bromine in 100 ml of methylene chloride. The bromine solution was added dropwise at a rate which maintained the reaction temperature in the range -55° to -50°. Addition of bromine required approximately 1.5 h, after which time the cooling bath was removed and the mixture stirred overnight at room temperature. The bulk of solvent was removed under vacuum at 45° and provided a residual mixture of a light yellow oil and ammonium bromide (white salt). This residue was shaken with 300 ml of ether, and then the ether extract was decanted. Sufficient water was added to the residue to dissolve the salt, and the resulting mixture was shaken with 100 ml of ether. The combined ethereal extracts were washed successively with 50 ml of saturated aqueous sodium carbonate and 50 ml of water. The wash water was tested for acidity (present in some runs) with universal indicator paper. If acidity was indicated, the aqueous base wash was repeated. The almost colorless ethereal solution was dried over anhydrous sodium

sulfate, filtered and freed from solvent under vacuum. Distillation of the oily residue afforded 85.3 g (87%) of pure colorless product. B.p., 70° at 0.6 mm (120); n_D^{25}, 1.4745. Anal. calcd. for $C_8H_{15}BrO_3$: C, 40.18; H, 6.28; Br, 33.42. Found: C, 40.32; H, 6.38; Br, 33.40. The n.m.r. spectrum of the product (Fig. 17) showed two signals in the anomeric (H-2) region at τ5.28 (envelope, W/2 ~3Hz) and τ5.71 (doublet, $J_{2,3}$=9.2 Hz) in the area ratio of 9:1, respectively.

G.l.c. analysis of the mixture (LII + LIV) on a column of 20% butanediol succinate on Gas Chrom P (1/8" x 12 ft column; helium flow rate 40 ml/min) at 195° showed two peaks in the ratio of 9:1.

Trans-2-methoxy-6-methoxymethyl-5,6-dihydro-2H-pyran (LV).

A quantity (47.8 g, 0.2 mole) of 3-bromo-2-methoxy-6-methoxymethyltetrahydropyran (LIII + LIV) was slowly added, through an addition funnel, to a stirred mixture of 32.4 g (0.6 mole) of sodium methoxide in 250 ml of methanol. During addition of the bromide the temperature of the reaction mixture rose to the boiling point of the solvent. A precipitate of sodium bromide accumulated. After all of the bromo compound had been added the reaction mixture was heated under reflux for 24 h. Thereafter the mixture was concentrated to 100 ml by fractional distillation

of the solvent. The mixture was cooled then shaken with 200 ml of ether. The supernatant liquid was decanted from the solid. Sufficient water was added to the residue to dissolve the solid material, and the resulting solution was extracted with two 50 ml portions of ether. The combined ethereal extracts were washed with three 25 ml portions of water, dried over anhydrous sodium sulfate, filtered and freed of solvent by distillation through a fractionating solumn. The residual slightly amber oil was distilled under reduced pressure to give 22.3 g (70%) of a pure colorless liquid. B.p., 84° at 200 mm (120); n_D^{25}, 1.4466. Anal. calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.77; Hz, 8.68. G.l.c. analysis showed a single broad peak. The 60 M. n.m.r. spectrum of the olefin (LV) showed a broad singlet in the anomeric (H-2) proton region at τ 5.20 (W/2=5 Hz). Under higher amplification a small signal (5% with respect to the signal at τ5.20) appeared at τ5.46 (narrow multiplet) which was assumed to be due to the cis isomer of LV.

Catalytic Hydrogenation of 2-Methoxy-6-methoxymethyl-5,6-dihydro-2H-pyran. (LV LVI)

Two grams (0.013 mole) of 2-methoxy-6-methoxymethyl-5,6-dihydro-2H-pyran in 75 ml of methyl alcohol containing 1 g

of sodium methoxide to prevent acid catalysed isomerization and 100 mg of 5% palladium on charcoal catalyst (Coleman, Matheson, Bell Co.) in a 500 ml heavy-walled hydrogenation bottle, was shaken under 50 p. s. i. of hydrogen for 24 h. The mixture was filtered and solvent removed under vacuum 45°. The residue was shaken with 100 ml of anhydrous ether and filtered. After removal of solvent by distillation, the residual oil was distilled in a semimicro distillation apparatus under reduced pressure to give 1.85 g (92) of reduction product. B.p., 108° at 75 mm; n_D^{24}, 1.4312. Lit. B.p., 110 at 75 mm; n_D^{25}, 1.4320 (for trans to cis isomeric mixture in the ratio 7:3) (93,103). G. l. c. and n. m. r. analyses of the hydrogenation product indicated the presence of essentially one component identical to (by g. l. c. and n. m. r.) 2-methoxy-6-methoxymethyltetrahydropyran. No signal was observed at τ5.65 (multiplet) which is characteristic (93,103) of the H-2 proton in the cis isomer.

Methyl-2, 3-anhydro-4-deoxy-6-O-methyl-α-DL-lyxo-hexopyranoside (LVIII) from trans-2-methoxy-6-methoxymethyl-5, 6-dihydro-2H-pyran (LV).

To 4.0 g (0.025 mole) of LV in 50 ml of anhydrous ether in a 250 ml three-neck round bottom flask, equipped with a

magnetic stirrer, and a condenser fitted with a drying tube, was added 6.6 g of 80% (0.03 mole) m-chloroperoxybenzoic acid. The solution was stirred for several days and was kept at ~35° by the heat of the magnetic stirring motor. When the solution had been stirred for 4 days a white precipitate of m-chlorobenzoic acid appeared. After a total of 7 days of reaction the mixture was cooled and filtered by suction. The residue was washed with two 25 ml portions of cold ether. The combined ethereal filtrates were washed with two 25 ml portions of saturated aqueous sodium carbonate solution and then with 25 ml of water. The combined washings were twice extracted with two 20 ml portions of ether. The combined ethereal filtrate and extracts (clear, colorless) were dried (Na_2SO_4), filtered, and the solvent removed by fractional distillation (spinning band column). The residual oil was distilled under reduced pressure to give 3.5 g (80%) of pure product. B.p., 64-66° at 0.5 mm (130°), (simple distillation) 78-80° at 2.5 mm (100); n_D^{25}, 1.4495. Anal. calcd. for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.93; H, 7.80.

G.l.c. analysis (20% butanediol succinate on Gas-Chrom P, Helium flow rate 50 ml per min. column temperature (80) showed a large peak with a small overlapping shoulder (>90:<10).

N. m. r. analysis showed two signals for the anomeric (H-1) proton at τ5.18 (singlet) and 5.04 (doublet) in the ratio of >95:<5 (see Fig. 11).

Methyl 4-deoxy-6-O-methyl-α-DL- arabino-hexopyranoside was prepared by a modification of a procedure by Černý (96).

A solution of 2.45 g (0.014 mole) of methyl 2,3-anhydro-4-deoxy-6-O-methyl-α-DL-lyxo-hexopyranoside (LVII) in 50 ml of 5% aqueous potassium hydroxide was heated under reflux for 24 h. To the cooled reaction mixture was added a solution of 2.5 ml of concentrated hydrochloric acid in 25 ml of water. The resulting slightly alkaline (pH ∿9) solution was continuously extracted with 150 ml of chloroform for 48 h. The chloroform extract was dried (Na_2SO_4), filtered and concentrated at 45° in a rotary evaporator. The residual syrup (2.35 g, 81%) resisted crystallization from ethyl acetate-hexane, methanol-ether, and hexane. The 60 M Hz n. m. r. spectrum of the syrup in $CDCl_3$ showed no signals (at τ5.18, singlet for H-1 and at τ7.10, doublet (J=4.0Hz) for H-2) which would indicate the presence of the epoxy starting material, LVII. A broad "singlet" for H-1 was observed at τ5.37 ($\frac{W}{2}$ ∿3 Hz). Two singlets due to the OCH_3 groups were observed at τ6.60 and at τ6.65. The proton

count was correct for methyl 4-deoxy-6-O-methyl-α-DL-arabino-hexopyranoside.

Di-p-nitrobenzoate of methyl-4-deoxy-6-O-methyl-α-DL-arabino-hexopyranoside.

A quantity (500 mg, 0.0026 mole) of p-nitrobenzoyl chloride was added to a mixture of 200 mg (0.001 mole) of syrupy methyl 4-deoxy-6-O-methyl-α-DL-arabino-hexopyranoside in 5 ml of anhydrous pyridine. The mixture was heated to boiling then poured on to 10 g of crushed ice whereupon a light yellow precipitate formed. The mixture was filtered under vacuum and the solid residue successively washed with 5 ml portions of water, 5% aqueous sodium carbonate and finally water. The solid was placed in 15 ml of boiling 95% ethanol and sufficient ethyl acetate was added dropwise to effect solution. The pale yellow crystals, which formed upon cooling the mixture overnight in a refrigerator, were collected by filtration under vacuum. After two additional recrystallizations as described above and drying for 24 h under vacuum (0.05 mm) at room temperature 300 mg of white prisms were obtained. M.p., 131-132°. Anal. calcd. for $C_{22}H_{22}O_{11}N_2$: C, 53.88; H, 4.52; N, 5.71. Found: C, 54.05; H, 4.77; N, 5.71.

The n.m.r. spectrum (100 M Hz) of the di-p-nitrobenzoate in $CDCl_3$ is shown in Fig. 23. The spin decoupling experi-

ment for this coupound is described in the Results and Discussion section, Chapter VII.

IX. PREPARATION OF METHYL 1,6-ANHYDRO-4-DEOXY-β-DL-XYLO-HEXOPYRANOSE.

2-Hydroxymethyl-3,4-dihydro-2H-pyran (LXV). was prepared by modification of a published procedure (24).

To a stirred, chilled (5°) solution of 33.6 (0.3 mole) of 3,4-dihydro-2H-pyran-2-carboxaldehyde in 300 ml of methanol was added, in small (ca. 1 g) portions, 8.3 g (0.3 mole) of sodium borohydride. After each addition the temperature rose to 10°. Before each succeeding addition of reducing agent the temperature of the reaction mixture was reduced to 5°. After all of the sodium borohydride had been added, the reaction mixture was allowed to come to room temperature and stirring was continued overnight. The reaction mixture was concentrated under reduced pressure with a rotary evaporator. Water (30 ml) was shaken with the residual syrup, which in turn was extracted with two 200 ml portions of methylene chloride. The combined extracts were dried (Na_2SO_4) filtered, freed of solvent and the oily residue was distilled under reduced pressure to give 31.4 g (92%) of pure product. B.p., 102° at 45 mm; n_D^{25}, 1.4772. Lit. B.p., 100-103° at 47 mm; n_D^{25}, 1.4764 (24).

6,8-Dioxabicyclo [3.2.1.] octane (LXVI).

To a stirred solution of 500 mg of p-toluenesulfonic acid in 500 ml of anhydrous benzene was gradually added 68 g (0.60 mole) of 2-hydroxymethyl-3,4-dihydro-2H-pyran. During addition of the alcohol heat was evolved. After the initial reaction had subsided the mixture was heated under reflux for 2 h, then cooled to room temperature. A slight excess of sodium methoxide (2 g) was added to neutralize the acid and the reaction mixture was stirred for 30 minutes. The solvent was removed by fractional distillation and the residue distilled under reduced pressure in a simple distillation apparatus. An air condenser was employed and the receiver was immersed in a dry ice-acetone bath. During distillation of the product it solidified in the condenser. The solid was melted with a heat lamp or hot air blower. The yield varied from 40% to 65%. B.p., 65° at 30 mm; M.p., 47-49° . Lit. b.p., 68-70° at 39 mm; m.p., 50° (97). Lit. b.p., 64-66° at 38 mm; m.p., 46-48° (98).

4-Bromo-6,8-dioxabicyclo [3.2.1.] octane (LXVII)

To an efficiently stirred mixture of 100 g (0.87 mole) of 6,8-dioxabicyclo [3.2.1] octane in 1000 ml of anhydrous carbon tetrachloride (dried over $CaCl_2$) and 300 g of powdered

anhydrous sodium carbonate was added, through an addition funnel, 139 g (0.87 mole) of bromine in 200 ml of anhydrous carbon tetrachloride. Consumption of bromine occurred most rapidly when the temperature of the reaction mixture was maintained at 35-40°. Below this temperature, the bromination proceeded slowly. Bromine was added in a rapid dropwise manner and a cold water bath was used to cool the reaction mixture, as required, to maintain the optimum temperature range of 35-40°. During addition of bromine a vigorous evolution of carbon dioxide was observed. The reaction mixture was stirred for 0.5 h after addition had been completed. Thereafter the reaction mixture was filtered under vacuum and the residue was washed with two 100 ml portions of methylene chloride. The combined filtrate and washings were divided into two equal portions and each treated in the following manner. The organic solution was washed successively with 150 ml of saturated aqueous, sodium carbonate and 100 ml of water. The combined washings were twice extracted with 100 ml of methylene chloride. The combined extracts were dried over anhydrous magnesium sulfate, filtered and freed of solvent on a rotary evaporator at 45°, under reduced pressure. The residual light amber colored oil was distilled under reduced

pressure to give a total of 115 g (73%) of pure colorless oil. (Yields varied in the range 60-75%). B. p., (a) 90° at 4.5 mm (125°),(b) 68° at 1 mm (105°); n_D^{27}, 1.5176. Anal. calcd. for $C_6H_9O_2Br$: C, 37.33; H, 4.69; Br, 41.39. Found: C, 37.53; H, 4.60; Br, 41.02.

G. l. c. analysis (F and M Model 700 using a 1/8" x 12' column packed with 20% butanediol succinate on Gas Chrom P (60-80 mesh) at a helium flow rate of 40 ml per min. and a column temperature of 190°), showed one symmetrical peak. (Under similar conditions cis- and trans-2-alkoxy-3-bromotetrahydropyrans are separated)

The 60 M Hz n. m. r. spectrum of LXVII in $CDCl_3$ (referred to tetramethylsilane) showed one sharp symmetrical peak at τ 4.60 due to H-5 (bicyclo numbering) which integrated for one proton. No other absorptions in the anomeric region were observed. A symmetrical envelope, characteristic of H-1, was observed centered at τ 5.45 (W/2-10Hz).

6,8-Dioxabicyclo [3.2.1.] octene (LXIV).

A quantity (70 g, 0.36 mole) of 4-bromo-6,8-dioxa-bicyclo [3.2.1]octane was added to a stirred mixture of 120 g of potassium hydroxide in 600 ml of 95% ethanol. The stirred

reaction mixture was heated under reflux for 24 h after which time the volume of the mixture was condensed to one half by fractional distillation of the solvent through a 30 cm Vigreux column. The cooled residue was filtered by vacuum and the residue washed with two 100 ml portions of ether. The filtrate and washings were combined and washed with two 50 ml portions of water. The amber colored organic solution was dried (Na_2SO_4), filtered and freed of the bulk of solvent by fractional distillation. The residual oil was distilled under reduced pressure to give 12 g (30%) of pure olefinic product and 35 g (50%) of unreacted starting material. B.p., 54° at 9 mm (84° at 50 mm); n_D^{25}, 1.4772. Anal. calcd. for $C_6H_8O_2$: C, 64.27; H, 7.19: Found: C, 64.07; H, 7.46. G.l.c. analysis (column temperature 150°) showed one symmetrical peak.

The 60 M Hz n.m.r. spectrum of LXIV showed signals at τ4.57 (envelope, W/2=5 Hz) for H-5 and absorptions in the (olefinic) region τ3.8 to τ4.4 integrating for two protons (H-3 and H-4).

1,6:2,3-Dianhydro-4-deoxy-β-DL-ribo-hexopyranose (LX).

A quantity (14.24 g, 0.066 mole) of 80% m-chloroperoxybenzoic acid was added to a magnetically stirred solution of 7.4 g (0.065 mole) of 6,8-dioxabicyclo [3.2.1]-3-octene in 150 ml

of anhydrous ether. After the solution was stirred at about 35° (due to heating of the magnetic stirring motor) for 4.5 days a white precipitate of m-chlorobenzoic acid gradually accumulated. After a total of 10 days of reaction under these conditions, the mixture was diluted with 100 ml of ether (which dissolved the precipitate) and extracted with two 50 ml portions of saturated aqueous sodium carbonate and 50 ml of water. The aqueous extracts were combined and retained. The ether portion was dried (Na_2SO_4), filtered and concentrated by fractionally distilling the solvent. This gave 1.5 g of a crude colorless oil. The aqueous portion was continuously extracted with chloroform (250 ml of solvent in the distillation flask) for 48 hrs. The chloroform extract was dried (Na_2SO_4), filtered and concentrated by fractional distillation to give 5.8 g of an oil. G.l.c. analysis (180°) of each of the oils obtained showed them to be identical. They contained one major component (95%) and a minor component (5%) shown as two slightly overlapping peaks. The combined oils were distilled under reduced pressure giving 6.05 g (80%)of a pure, colorless product which spontaneously solidified in the receiver. B.p., 62° at 0.8 mm (90°); n_D^{25}, 1.4809. M.p., 24-26°. Anal. calcd. for

$C_6H_8O_3$: C, 56.25; H, 6.29. Found: C, 56.38; H, 6.60.

The compound (LX) was readily soluble in water, chloroform ether and alcohol.

A detailed analysis of the n.m.r. spectrum of LX, which is shown in Figs. 18 and 19, and is presented in the Results and Discussion section, Chapter VIII.

1,6-Anhydro-4-deoxy-β-DL-xylo-hexopyranose (LXI).

1,6:2,3-Dianhydro-4-deoxy-β-DL-ribo hexopyranose (LX) (1.20 g, 0.0093 mole) was heated under reflux in 50 ml of 5% aqueous potassium hydroxide for 24 h. To the cooled reaction mixture was added a solution of 2.5 ml of concentrated hydrochloric acid in 10 ml of water, resulting in a slightly alkaline (pH~9) solution. The reaction mixture was continuously extracted for 48 h. with chloroform (150 ml still pot volume). The chloroform extract was dried (Na_2SO_4), filtered and freed of solvent with a rotary evaporator under reduced pressure at 45°. The syrupy residue was dissolved in a minimum of ethyl acetate (ca. 15 ml). The solution was heated to boiling and filtered while hot. Three times, 30 ml of Skellysolve B (hexane) was added to the ethyl acetate solution and the volume of the mixture reduced to 15 ml by concentration on a hot plate. Finally, 25 ml

Skellysolve B was added and the mixture was heated to boiling then allowed to come to room temperature during which time fine white crystals accumulated. The mixture stood at room temperature overnight and crystals collected by filtration under vacuum. The crystals, which were hygroscopic, were dried overnight over calcium sulfate at room temperature under 0.5 mm pressure, giving 0.60 g of pure product. Concentration of the filtrate to half the original volume (on a hot plate) and allowing the mixture to cool to room temperature, afforded an additional 0.35 g of pure product (total yield, 70%). M.p., 155-156° Lit. (D-enantiomer) m.p., 155-157 (96). Anal. calcd. for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 48.90; H, 6.90.

Di-p-nitrobenzoate ester of LXI

To a solution of 300 mg of LXI in 5 ml of pyridine was added 1.12 g of p-nitrobenzoyl chloride. While the mixture was continuously agitated it was heated on a hot plate until the solvent began to boil. The mixture was then poured on to 25 g of crushed ice, whereupon a solid formed. After all of the ice had melted, the solid was collected by filtration under vacuum, washed with dilute (5%) aqueous sodium carbonate, then with water. The crude derivative was placed in 15 ml of boiling methanol and

sufficient ethyl acetate was added, dropwise, to effect solution. When the solution had cooled slightly, some decoloring charcoal was added and the mixture was heated to boiling. The hot mixture was filtered and then allowed to attain room temperature during which time pale yellow needles formed. Two more recrystallizations and drying under vacuum gave 800 mg of the pure di-p-nitrobenzoate. M.p., 196-198°. Lit. (for the D-enantiomer) m.p., 218-219°(96). Anal. calcd. for $C_{20}H_{16}O_{10}N_2$: C, 54.06; H, 3.63; N, 6.31. Found: C, 54.05; H, 3.87; N, 6.21.

The 100 M Hz n.m.r. spectrum of the di-p-nitrobenzoate of DL-LXI in $CDCl_3$ solution and that of an authentic sample* of the pure ester of D-LXI were superimposable.

* The author is indepted to M. Černý for authentic samples of 1,6-anhydro-4-deoxy-β-D-arabino-hexopyranoside and its di-p-nitro-benzoate, and the di-p-nitrobenzoate ester of 1,6-anhydro-4-deoxy-β-D-xylo-hexopyranoside (D-LXI)

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APPENDIX

The following is a list of publications taken from this thesis and from other investigations by the author while work for this thesis was in progress.

1. 2-Alkoxy-3-hydroxytetrahydropyrans and 2-alkoxy-3-hydroxytetrahydrofurans. I. Preparation, structure, and some derivatives. F. Sweet and R. K. Brown, Can. J. Chem. 44, 1571 (1966).

2. A convenient methylation procedure. U. E. Diner, F. Sweet, and R. K. Brown, Can. J. Chem. 44, 1591 (1966).

3. Models to obtain spin-spin couplings for the anomeric proton of 2,3-dialkoxytetrahydropyrans (cis- and trans-tetrahydropyrano-[2,3-b]-1,4-dioxane.) F. Sweet and R. K. Brown, Can. J. Chem. 45, 1007 (1967).

4. Hydrogen bonding and conformation in cis- and trans-2-alkoxy-3-hydroxytetrahydrofurans. W. W. Zajac, Jr., F. Sweet, and R. K. Brown, Can. J. Chem. 46, 21 (1968).

5. Stereochemical vs polar control in the preparation and $LiAlH_4$ reduction of cis- and trans-2-alkoxy-3,4-epoxytetrahydropyrans. F. Sweet and R. K. Brown, Can. J. Chem. 46 (1968) (in press).

6. Bromination of 2-ethoxy-5,6-dihydro-2H-pyran and base catalyzed dehydrohalogenation of the product.

F. Sweet and R. K. Brown, Can. J. Chem. 46 (1968) (submitted).

7. Models for the assignment of the chemical shifts for protons on the epoxide ring of 2,3-anhydroglycopyranosides.

F. Sweet and R. K. Brown, Can. J. Chem. 46 (1968) (in press).

8. The preparation of methyl 4-deoxy-3-O-methyl-α,β-DL-threo-pentopyranoside.

F. Sweet and R. K. Brown, Can. J. Chem. 46 (1968) (in press).

9. Cis- and trans-2,4-dimethoxytetrahydropyran. (Models for the study of the anomeric effect.)

F. Sweet and R. K. Brown, Can. J. Chem. 46 (1968) (in press).

10. Synthesis of methyl 2,3-anhydro-4-deoxy-6-O-methyl-α-DL-lyxo-hexopyranoside.

F. Sweet and R. K. Brown, Can. J. Chem. 46 (1968) (submitted).

11. The Synthesis of 1,6-anhydro-4-deoxy-β-DL-xylo-hexopyranose.

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